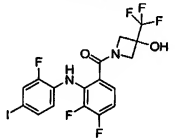
EXAMPLE 8(n): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-methyl-1*H*-imidazol-2-yl)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.34 (dd, 1H), 7.31-7.25 (m, 1H), 7.23-7.18 (m, 1H), 7.11-7.09 (m, 1H), 7.06-6.97 (m, 1H), 6.89-6.86 (m, 1H), 6.62-6.55 (m, 1H), 4.88-4.80 (m, 1H), 4.52-4.44 (m,1H), 4.38-4.30 (m, 1H), 4.21-4.12 (m, 1H), 3.68 (s, 3H). MS (EI) for $C_{20}H_{16}F_3IN_4O_2$: 529 (MH^+).

EXAMPLE 9

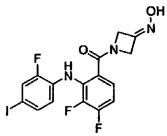
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(trifluoromethyl)azetidin-3-ol



[00349] 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-one (25 mg, 0.056 mmol), prepared using procedures described in Example 6, was taken into DMF (0.5 mL) followed by addition of (trifluoromethyl)trimethylsilane (40 μL, 0.28 mmol) and cesium carbonate (22 mg, 0.067mmol) and the mixture was stirred for one hour at room temperature. The mixture was partitioned with ethyl ether and water and the organic phase washed three times with additional water then brine and dried over anhydrous sodium sulfate. Filtration and concentration followed by silica gel flash chromatography of the residue using hexanes:ethyl acetate 3:2 as eluent afforded 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(trifluoromethyl)azetidin-3-ol (19.8 mg, 69% yield) as a colorless crystalline solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.31-8.26 (br, 1H), 7.40 (d, 1H), 7.33 (d, 1H), 7.13-7.10 (m, 1H), 6.86-6.80 (m, 1H), 6.65-6.60 (m, 1H), 4.42 (br s, 2H), 4.18 (br s, 2H). MS (EI) for $C_{17}H_{11}F_6IN_2O_2$: 517 (MH^+).

EXAMPLE 10

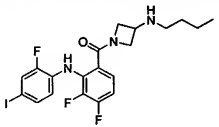
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-one oxime



[00350] To a solution of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-one (100 mg, 0.22 mmol), prepared using procedures similar to those described in Example 6, in dioxane (1.0 mL) was added hydroxylamine (0.10 mL, 50% solution in water, 1.5 mmol), and the resulting solution was heated at 60 °C for 18 h. The mixture was cooled to room temperature and the crude product was purified by reverse phase HPLC to afford 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-one oxime (56 mg, 54% yield): ^{1}HNMR (400MHz, $CDCl_3$), 8.43 (br s), 7.43-7.39 (m, 2H), 7.35-7.32 (dd,1H), 7.19-7.15 (m, 1H), 6.87-6.81 (m,1H), 6.65-6.59 (m, 1H), 4.89 (br s, 2H), 4.85 (br s, 2H); MS (EI) for $C_{16}H_{11}F_3IN_3O_2$: 462 (MH^+).

Example 11

***N*-butyl-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine**

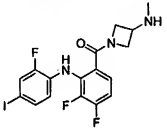


[00351] To a solution of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine (0.09 M in acetonitrile, 500 μL, 0.045 mmol), prepared using procedures similar to those described in Example 2, was added triethylamine (20 μL, 0.135 mmol) and *n*-butylbromide (6.14 μL, 0.054 mmol) followed by additional acetonitrile (1.0 mL). The reaction mixture was stirred at room temperature for 16 h, at which time it was purified directly by reverse phase

HPLC to afford the title compound (8.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$): 8.50 (s, 1H), 7.39 (dd, 1H), 7.32 (dd, 1H), 7.13-7.09 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.57 (m, 1H), 4.35 (br s, 2H), 4.00 (br s, 1H), 3.87 (br s, 1H), 3.74-3.68 (m, 1H), 3.20 (br s, 3.5H), 2.56 (t, 2H), 2.03 (s, 2H), 1.50-1.42 (m, 2H), 1.39-1.29 (m, 2H), 0.91 (t, 3H). MS (EI) for $C_{20}H_{21}F_3IN_3O$: 504 (MH^+).

EXAMPLE 12

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-methylazetidin-3-amine



[00352] To a solution of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine (0.10 M in acetonitrile, 1.0 mL, 0.09 mmol), prepared using procedures similar to those described in Example 2, in 1:1 ratio of methanol and tetrahydrofuran (2.0 mL) was added formaldehyde (37%wt, 6.7 μL, 0.09 mmol) followed by sodium cyanoborohydride (11.0 mg, 0.18 mmol). The reaction mixture was stirred at room temperature for 16 h, at which time it was quenched with saturated aqueous ammonium chloride. The solution was then purified directly by reverse phase HPLC to afford the title compound (14.9 mg). ^{1}H NMR (400 MHz, $CDCl_3$): 8.13 (br s, 1H), 7.35 (d, 1H), 7.30 (d, 1H), 7.09-7.04 (m, 1H), 6.84-6.78 (m, 1H), 6.60-6.54 (m, 1H), 4.46-4.33 (br m, 4H), 3.93 (br m, 1H), 2.64 (s, 3H). MS (EI) for $C_{17}H_{15}F_3IN_3O$: 462 (MH^+).

[00353] Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compounds of the invention were prepared:

EXAMPLE 12(a). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-methylazetidin-3-amine: ^{1}H NMR (400 MHz, $CDCl_3$): 8.13 (br s, 1H), 7.35 (d, 1H), 7.30 (d, 1H), 7.09-7.04 (m, 1H), 6.84-6.78 (m, 1H), 6.60-6.54 (m, 1H), 4.46-4.33 (br m, 4H), 3.93 (br m, 1H), 2.64 (s, 3H). MS (EI) for $C_{17}H_{15}F_3IN_3O$: 462 (MH^+).

EXAMPLE 12(b). 2-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]amino}ethanol: ^{1}H NMR (400 MHz, $CDCl_3$): 8.20 (s, 1H), 7.36 (d, 1H), 7.30 (d, 1H), 7.13-7.09 (m, 1H), 6.85-6.79 (m, 1H), 6.61-6.55 (m, 1H), 4.43 (br m, 3H), 3.98 (br m, 1H), 3.87 (br m, 1H), 3.02 (br m, 1H), 1.24-1.20 (m, 1H). MS (EI) for $C_{18}H_{17}F_3IN_3O_2$: 492 (MH^+).

EXAMPLE 12(c). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]propane-1,3-diamine: ^{1}H NMR (400 MHz, $CDCl_3$): 8.51 (s, 1H), 7.39 (d, 1H), 7.32 (d, 1H), 7.14-7.10 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.57 (m, 1H), 4.33 (br s, 2H), 3.99 (br s, 1H), 3.84 (br s, 1H), 3.71-3.64 (m, 1H), 2.91 (t, 2H), 2.70-2.66 (m, 2H), 2.01 (s, 4H), 1.76-1.69 (m, 2H). MS (EI) for $C_{19}H_{20}F_3IN_4O$: 505 (MH^+).

EXAMPLE 12(d). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-ethylazetidin-3-amine: ^{1}H NMR (400 MHz, $CDCl_3$): 8.47 (s, 1H), 7.38 (d, 1H), 7.31 (d, 1H), 7.13-7.09 (m, 1H), 6.83-6.77 (m, 1H), 6.62-6.57 (m, 1H), 4.49 (br s, 3H), 4.36 (br s, 2H), 4.08 (br s, 1H), 3.94 (br s, 1H), 3.77-3.72 (m, 1H), 2.69-2.63 (m, 2H), 1.99 (s, 2H), 1.14 (t, 3H). MS (EI) for $C_{18}H_{17}F_3IN_3O$: 476 (MH^+).

EXAMPLE 12(e). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2-methylpropyl)azetidin-3-amine: ^{1}H NMR (400 MHz, $CDCl_3$): 8.50 (s, 1H), 7.38 (d, 1H), 7.31 (d, 1H), 7.14-7.09 (m, 1H), 6.83-6.76 (m, 1H), 6.63-6.57 (m, 1H), 4.34 (br s, 2H), 4.00 (br s, 1H), 3.86 (br s, 1H), 3.71-3.66 (m, 1H), 3.42 (br s, 2H), 2.36 (d, 2H), 2.00 (s, 1H), 1.75-1.65 (m, 1H), 0.91 (d, 6H). MS (EI) for $C_{20}H_{21}F_3IN_3O$: 504 (MH^+).

EXAMPLE 12(f). *N*-(cyclopropylmethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine: ^{1}H NMR (400 MHz, $CDCl_3$): 8.48 (s, 1H), 7.39 (d, 1H), 7.32 (d, 1H), 7.13-7.09 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.57 (m, 1H), 5.78 (s, 3H), 4.36 (br s, 2H), 4.10 (br s, 1H), 3.94 (br s, 1H), 3.81-3.75 (m, 1H), 2.49 (d, 2H), 2.01 (s, 4H), 0.94-0.86 (m, 1H), 0.53 (d, 2H), 0.13 (d, 2H). MS (EI) for $C_{20}H_{19}F_3IN_3O$: 502 (MH^+).

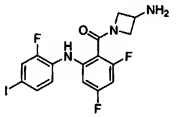
EXAMPLE 12(g). *N*-(cyclohexylmethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine: ^{1}H NMR (400 MHz, $CDCl_3$): 8.48 (s, 1H), 7.38 (dd, 1H), 7.31 (d, 1H), 7.13-7.08 (m, 1H), 6.83-6.77 (m, 1H), 6.63-6.57 (m, 1H), 4.55 (br s, 2H), 4.33 (br m, 2H), 4.02 (br s, 1H) 3.87 (br s, 1H), 3.71-

3.65 (m, 1H), 2.38 (d, 2H), 1.74-1.68 (m, 4H), 1.46-1.36 (m, 1H), 1.27-1.12 (m, 3H), 0.94-0.84 (m, 2H). MS (EI) for $C_{23}H_{25}F_3IN_3O$: 544 (MH^+).

EXAMPLE 12(h). *N*-(cyclopentylmethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine: ^{1}H NMR (400 MHz, $CDCl_3$): 8.32 (s, 1H), 7.37 (d, 1H), 7.31 (d, 1H), 7.11-7.07 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.57 (m, 1H), 4.44-4.37 (m, 3H), 4.02-3.96 (m, 1H), 2.84 (d, 2H), 2.54 (br s, 5H), 2.20-2.12 (m, 1H), 1.88-1.81 (m, 2H), 1.68-1.54 (m, 4H), 1.24-1.15 (m, 2H). MS (EI) for $C_{22}H_{23}F_3IN_3O$: 530 (MH^+).

EXAMPLE 13

1-({2,4-difluoro-6-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine



[00354] 2,4,6-Trifluorobenzoic acid (643 mg, 3.65 mmol) and 2-fluoro-4-iodoaniline (1.0 g, 4.22 mmol) were taken into acetonitrile (30 mL) followed by addition of lithium amide (290 mg, 12.7 mmol) and the mixture was heated to 60 °C under a nitrogen atmosphere for one hour. On cooling to room temperature the mixture was added to 1 N aqueous hydrochloric acid (100 mL) and the precipitate formed was collected by filtration and washed once with water then hexanes and dried *in vacuo* to give 2,4-difluoro-6-[(2-fluoro-4-iodophenyl)amino]benzoic acid (849 mg, 59% yield) as a tan solid. ^{1}H-NMR (400 MHz, D_6-DMSO): 13.72 (br s, 1H), 9.46 (s, 1H), 7.75 (d, 1H), 7.56 (d, 1H) 7.28 (tr, 1H), 6.73-6.67 (m, 1H), 6.53 (d, 1H).

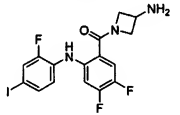
[00355] 2,4-Difluoro-6-[(2-fluoro-4-iodophenyl)amino]bcnzoic acid (100 mg, 0.25 mmol) was taken into DMF (1 mL) followed by addition of PyBOP (137 mg, 0.26 mmol) and the mixture was stirred for 15 minutes then NMM (60 μL, 0.5 mmol) and commercially available 1,1-dimethylethyl azetidin-3-ylcarbamate (43 mg, 0.25 mmol) were subsequently added. The mixture was allowed to stir for 12 hours at room temperature then partitioned with ethyl acetate and water. The organic phase was washed three times with additional water then brine and dried over anhydrous sodium sulfate. Filtration and concentration followed by silica gel flash chromatography of

the residue using hexanes:ethyl acetate 3:1 as eluent afforded 1,1-dimethylethyl [1-({2,4-difluoro-6-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]carbamate (125 mg) as a colorless oil.

[00356] The oil was taken into trifluoroacetic acid (1 mL) and allowed to stand at room temperature for 5 minutes then concentrated *in vacuo*. The residue was portioned with ethyl acetate and saturated aqueous sodium bicarbonate and the organic phase washed with brine then dried over anhydrous sodium sulfate. The organic solution was filtered and concentrated then the residue taken into methanol (1 mL) followed by addition of 4 N HCl in dioxane until the solution was acidic. The solution was concentrated and the residue triturated with ethyl ether to give a thick precipitate. The solid was collected by filtration and dried *in vacuo* to give 1-({2,4-difluoro-6-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine hydrochloride (58 mg, 48% overall yield). ^{1}H-NMR (400 MHz, D_6-DMSO): 8.67 (br s, 3H), 8.45 (s, 1H), 7.71 (d, 1H), 7.54 (d, 1H), 7.25 (tr, 1H), 6.77 (tr, 1H), 6.48 (d, 1H), 4.28-4.23 (m, 2H), 4.13-4.06 (m, 3H). MS (EI) for $C_{16}H_{13}F_3IN_3O$: 448 (MH^+).

EXAMPLE 14

1-({4,5-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine

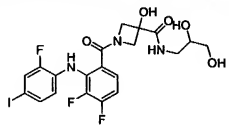


[00357] 2,4,5-Trifluorobenzoic acid (643 mg, 3.65 mmol) and 2-fluoro-4-iodoaniline (1.0 g, 4.22 mmol) were taken into acetonitrile (30 mL) followed by addition of lithium amide (290 mg, 12.7 mmol) and the mixture was heated to 60 °C under a nitrogen atmosphere for one hour. On cooling to room temperature the mixture was added to 1 N aqueous hydrochloric acid (100 mL) and the precipitate formed was collected by filtration and washed once with water then hexanes and dried *in vacuo* to give 4,5-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid (624 mg, 43% yield) as a tan solid. ^{1}H-NMR (400 MHz, D_6-DMSO): 13.65 (br s, 1H), 9.63 (s, 1H), 7.84 (tr, 1H), 7.71 (d, 1H), 7.52 (d, 1H), 7.32 (tr, 1H), 7.03-6.98 (dd, 1H).

[00358] 4,5-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid (100 mg, 0.25 mmol) was taken into DMF (1 mL) followed by addition of PyBOP (137 mg, 0.26 mmol) and the mixture was stirred for 15 minutes then NMM (60 μL, 0.5 mmol) and commercially available 1,1-dimethylethyl azetidin-3-ylcarbamate (43 mg, 0.25 mmol) were subsequently added. The mixture was allowed to stir for 12 hours at room temperature then partitioned with ethyl acetate and water. The organic phase was washed three times with additional water then brine and dried over anhydrous sodium sulfate. Filtration and concentration followed by silica gel flash chromatography of the residue using hexanes:ethyl acetate 3:1 as eluent afforded 1,1-dimethylethyl [1-({4,5-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]carbamate (131 mg) as a colorless oil. The oil was taken into trifluoroacetic acid (1 mL) and allowed to stand at room temperature for 5 minutes then concentrated *in vacuo*. The residue was portioned with ethyl acetate and saturated aqueous sodium bicarbonate and the organic phase washed with brine then dried over anhydrous sodium sulfate. The organic solution was filtered and concentrated then the residue taken into methanol (1 mL) followed by addition of 4 N HCl in dioxane until the solution was acidic. The solution was concentrated and the residue triturated with ethyl ether to give a thick precipitate. The solid was collected by filtration and dried *in vacuo* to give 1-({4,5-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine hydrochloride (67 mg, 55% overall yield). ^{1}H-NMR (400 MHz, D_6-DMSO): 9.02 (s, 1H), 8.54 (br s, 3H), 7.68 (dd, 1H), 7.53-7.47 (m, 2H), 7.22 (tr, 1H), 7.16 (dd, 1H), 4.60 (br s, 1H), 4.23 (br s, 2H), 4.03 (br m, 2H). MS (EI) for $C_{16}H_{13}F_3IN_3O$: 448 (MH^+).

EXAMPLE 15

1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2,3-dihydroxypropyl)-3-hydroxyazetidine-3-carboxamide



[00359] 1-(Diphenylmethyl)azetidin-3-ol hydrochloride (2.75 g, 9.98 mmol), prepared using procedures similar to those described for **Scheme 1** of the General Synthetic Section, 3Å molecular sieves and 4-methylmorpholine (1.1 mL, 10.0 mmol) were suspended in dichloromethane (20 mL) at 0 °C. 4-Methylmorpholine N-oxide (2.93 g, 25.0 mmol) and tetrapropylammonium perruthenate (140 mg, 0.399 mmol) were added and the mixture was stirred at ambient for 24 h. The mixture was filtered through a plug of silica using 5% triethylamine in ethyl acetate as eluent. The filtrate was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 8:1 hexanes:ethyl acetate) gave 1-(diphenylmethyl)azetidin-3-one (871 mg, 3.68 mmol, 37% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 7.50-7.46 (m, 4H), 7.33-7.27 (m, 4H), 7.27-7.19 (m, 2H), 4.59 (s, 1H), 4.01 (s, 4H); MS (EI) for $C_{16}H_{15}NO$: 238 (MH^+).

[00360] 1-(Diphenylmethyl)azetidin-3-one (600 mg, 2.53 mmol), was dissolved in dichloromethane (1 mL) and treated with triethylamine (0.5 mL, 3.59 mmol) and trimethylsilylcyanide (0.8 mL, 6.01 mmol) at ambient for 2 h and then the mixture was concentrated *in vacuo* to afford 1-(diphenylmethyl)-3-[(trimethylsilyl)oxy]azetidine-3-carbonitrile (774 mg, 2.30 mmol, 91% yield) as a yellow solid. 1-(diphenylmethyl)-3-[(trimethylsilyl)oxy]azetidine-3-carbonitrile (250 mg, 0.744 mmol) was dissolved in dichloromethane (2 mL) at 0 °C and concentrated sulfuric acid (0.2 mL) was added dropwise. The mixture was stirred at ambient for 2 h and then was cooled to 0 °C and 25% ammonium hydroxide solution was added carefully dropwise to pH ~10-11. The mixture was extracted twice with dichloromethane. The combined organic portion was washed with brine, dried over

anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford a residue which was triturated with hexanes/ether to afford 1-(diphenylmethyl)-3-hydroxyazetidine-3-carboxamide (160 mg, 0.567 mmol, 76% yield) as an off-white solid: ^{1}H NMR (400 MHz, $CDCl_3$): 7.92 (br s, 1H), 7.39-7.34 (m, 4H), 7.33-7.27 (m, 4H), 7.27-7.19 (m, 2H), 5.61 (br s, 1H), 4.45 (s, 1H), 4.34 (s, 1H), 3.50 (dd, 2H), 3.20 (dd, 2H); MS (EI) for $C_{17}H_{18}N_2O_2$: 283 (MH^+).

[00361] 1-(Diphenylmethyl)-3-hydroxyazetidine-3-carboxamide (1.1 g, 3.90 mmol) was treated with 10% sodium hydroxide in ethanol (15 mL) and water (2 mL) at reflux for 2 h and then was concentrated *in vacuo*. The resiude was neutralized with 1 N hydrochloric acid (pH ~7) and the precipitate was collected by filtration and lyophilized to afford 1-(diphenylmethyl)-3-hydroxyazetidine-3-carboxylic acid (assume 3.90 mmol) which was used without further purification: ^{1}H NMR (400 MHz, d_6-DMSO): 7.45-7.40 (m, 4H), 7.31-7.25 (m, 4H), 7.21-7.15 (m, 2H), 4.52 (s, 1H), 3.46 (dd, 2H), 3.02 (dd, 2H); MS (EI) for $C_{17}H_{17}NO_3$: 284 (MH^+).

[00362] 1-(Diphenylmethyl)-3-hydroxyazetidine-3-carboxylic acid (assume 3.90 mmol) was suspended in methanol (40 mL) and 4 N hydrochloric acid in dioxane (1 mL, 4 mmol) was added. 20 wt% Palladium hydroxide on carbon (100 mg) was added to the solution and the mixture was treated with hydrogen at 40 psi for 2 h. The mixture was filtered and the filtrate was concentrated *in vacuo* to afford 3-hydroxyazetidine-3-carboxylic acid hydrochloride which was dissolved in tetrahydrofuran (5 mL) and water (5 mL) and treated with potassium carbonate (1.615 g, 11.7 mmol) and di-*tert*-butyl dicarbonate (935 mg, 4.29 mmol) were added. The mixture was stirred at ambient for 17 h and then the mixture was partitioned between ethyl acetate and water. The aqueous portion was extracted with ethyl acetate and then was acidified to pH ~3-4 and extracted twice more with ethyl acetate. The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford 1-{[(1,1-dimethylethyl)oxy]carbonyl}-3-hydroxyazetidine-3-carboxylic acid which was dissolved in DMF (3 mL). Benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (2.028 g, 3.90 mmol) and *N,N*-diisopropylethylamine (0.7 mL, 4.03 mmol) were added. The mixture was stirred at ambient for 5 minutes and then allylamine (0.6 mL, 8.03 mmol) was added and the mixture was stirred for 17 h. The mixture was partitioned between ethyl acetate and 5% lithium chloride. The organic portion was washed with 20% citric acid, saturated sodium bicarbonate and brine,

then was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, ethyl acetate) gave 1,1-dimethylethyl 3-hydroxy-3-[(prop-2-en-1-ylamino)carbonyl]azetidine-1-carboxylate (782 mg, 3.05 mmol, 78% yield from 1-(diphenylmethyl)-3-hydroxyazetidine-3-carboxamide). 1,1-Dimethylethyl 3-hydroxy-3-[(prop-2-en-1-ylamino)carbonyl]azetidine-1-carboxylate (782 mg, 3.05 mmol) was dissolved in methanol (10 mL) and 4 N hydrochloric acid in dioxane (2 mL, 8 mmol) was added. The mixture was refluxed for 15 minutes and then was concentrated *in vacuo* to afford 3-hydroxy-*N*-prop-2-en-1-ylazetidine-3-carboxamide hydrochloride (3.05 mmol).

[00363] 3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid (1.20 g, 3.05 mmol), prepared using procedures similar to those described in US 7,019,033, 4-(dimethylamino)pyridine (1.20 g, 9.86 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (701 mg, 3.66 mmol) were dissolved in DMF (10 mL). The mixture was stirred at ambient for 5 minutes and then 3-hydroxy-*N*-prop-2-en-1-ylazetidine-3-carboxamide hydrochloride (3.05 mmol) in DMF (5 mL) was added and the mixture was stirred for 15 h. The mixture was partitioned between ethyl acetate and 5% lithium chloride. The organic portion was washed with 20% citric acid, saturated sodium bicarbonate and brine, then was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 60-85% ethyl acetate in hexanes) and then reverse phase HPLC gave 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxy-*N*-prop-2-en-1-ylazetidine-3-carboxamide (150 mg, 0.282 mmol, 9% yield): ^{1}H NMR (400 MHz, d_6-DMSO): 8.64 (br s, 1H), 8.13 (t, 1H), 7.58 (dd, 1H), 7.38 (dd, 1H), 7.34-7.28 (m, 1H), 7.21-7.12 (m, 1H), 6.84 (br s, 1H), 6.72 (ddd, 1H), 5.83-5.72 (m, 1H), 5.10-4.99 (m, 2H), 4.38 (d, 1H), 4.20 (d, 1H), 4.02 (d, 1H), 3.86 (d, 1H), 3.73-3.68 (m, 2H); MS (EI) for $C_{20}H_{17}F_3IN_3O_3$: 532 (MH^+).

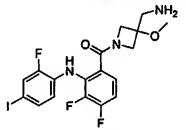
[00364] 1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxy-*N*-prop-2-en-1-ylazetidine-3-carboxamide (88 mg, 0.166 mmol) and 4-methylmorpholine *N*-oxide (58 mg, 0.496 mmol) were dissolved in acetone / water (4:1; 10 mL) and osmium tetroxide (2.5 wt.% in water; 0.1 mL) was added. The solution was stirred at ambient for 15 h, then was quenched with saturated sodium bisulfite (2 mL) and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and brine. The aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over anhydrous sodium

sulfate, filtered and concentrated *in vacuo*. Purification by reverse phase HPLC gave 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2,3-dihydroxypropyl)-3-hydroxyazetidine-3-carboxamide (68 mg, 0.120 mmol, 72% yield): ^{1}H NMR (400 MHz, d_6-DMSO): 8.65 (br s, 1H), 7.72 (t, 1H), 7.58 (dd, 1H), 7.41-7.36 (m, 1H), 7.34-7.28 (m, 1H), 7.21-7.12 (m, 1H), 6.92 (br s, 1H), 6.72 (ddd, 1H), 5.00-4.10 (br, 2H), 5.10-4.99 (m, 2H), 4.39 (d, 1H), 4.20 (d, 1H), 4.02 (d, 1H), 3.54-3.45 (m, 1H), 3.34-3.21 (m, 2H), 3.06-2.96 (m, 1H); MS (EI) for $C_{20}H_{19}F_3IN_3O_5$: 566 (MH^+).

[00365] EXAMPLE 15(a). Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compounds of the invention were prepared: 1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidine-3-carboxamide: ^{1}H NMR (400 MHz, d_6-DMSO): 8.63 (br s, 1H), 7.58 (dd, 1H), 7.42-7.36 (m, 3H), 7.34-7.28 (m, 1H), 7.22-7.12 (m, 1H), 6.76-6.68 (m, 2H), 4.39 (d, 1H), 4.19 (d, 1H), 4.00 (d, 1H), 3.83 (d, 1H); MS (EI) for $C_{17}H_{13}F_3IN_3O_3$: 492 (MH^+).

EXAMPLE 16

6-{[3-(aminomethyl)-3-(methyloxy)azetidin-1-yl]carbonyl}-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline



[00366] Phenylmethyl 1-oxa-5-azaspiro[2.3]hexane-5-carboxylate (165 mg, 0.75 mmol), prepared using procedures similar to those described in Reference 3, in THF (1 mL) was added to anhydrous ammonia saturated in THF (10 mL) and the mixture was allowed to stir in a sealed vessel at room temperature over 24 hours. The solution was then concentrated and taken back into THF (1 mL) followed by addition of di-*tert*-butyldicarbonate (164 mg, 0.75 mmol) and stirred for one hour at room temperature. The mixture was then concentrated and the residue purified by silica gel flash chromatography using hexanes:ethyl acetate (1:1) as eluent to give phenylmethyl 3-[({[(1,1-dimethylethyl)oxy]carbonyl}amino)methyl]-3-

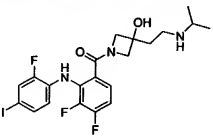
hydroxyazetidine-1-carboxylate (16.5 mg, 7% yield) and unreacted epoxide (120 mg, 73% recovery). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.34 (m, 5H), 5.10 (br, 1H), 5.09 (s, 2H), 4.68 (s, 1H), 3.90 (dd AB, 4H), 3.41 (d, 2H), 1.44 (s, 9H).

[00367] Phenylmethyl 3-[({[(1,1-dimethylethyl)oxy]carbonyl}amino)methyl]-3-hydroxyazetidine-1-carboxylate (16.5 mg, 0.05 mmol) and 10% Pd/C (8 mg) were taken into methanol (2 mL) and hydrogenated at ambient pressure over 12 hours. The catalyst was removed by filtration and the filtrate concentrated and dried *in vacuo*. The residue was taken into THF (1 mL) followed by addition of DIPEA (10 μL, 0.06 mmol) and 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoyl fluoride (19.8 mg, 0.05 mmol), prepared using procedures similar to those described in Reference 1, and the solution was stirred at room temperature for 30 minutes. Concentration and purification of the residue by silica gel flash chromatography using hexanes:ethyl acetate (1:1.5) afforded 1,1-dimethylethyl {[1-({3,4-difluoro-2[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidine-3-yl]methyl}carbamate (19 mg, 66% yield).

[00368] 1,1-Dimethylethyl {[1-({3,4-difluoro-2[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidine-3-yl]methyl}carbamate (8.0 mg, 0.014 mmol) and silver (I) oxide (12 mg, 0.05 mmol) were taken into methyl iodide (0.5 mL) and the mixture was brought to reflux for 4 hours. The suspension was then cooled to room temperature and diluted with an excess of ethyl ether then filtered. The filtrate was concentrated and purified by silica gel flash chromatography using hexanes:ethyl acetate (1:1) as eluent to give 1,1-dimethylethyl {[1-({3,4-difluoro-2[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(methyloxy)azetidine-3-yl]methyl}carbamate (2 mg). The material was taken into TFA (0.5 mL) and allowed to stand for 5 minutes then concentrated *in vacuo*. The residue was azetroped twice from methanol (2 mL) and the residue dried *in vacuo* to afford 6-{[3-(aminomethyl)-3-(methyloxy)azetidin-1-yl]carbonyl}-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline trifluoroacetate salt (2.3 mg, 27% yield) as an amorphous solid. MS (EI) for $C_{18}H_{17}F_3IN_3O$: 492 (MH^+).

EXAMPLE 17

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{2-[(1-methylethyl)amino]ethyl}azetidin-3-ol



[00369] A solution of *tert*-butyl acetate (566 μL, 4.2 mmol) in THF (10 mL) was cooled to -78 °C. To the solution was added LHMDS (5.25 mL of a 1.0 M solution in hexanes, 5.25 mmol), and the resulting mixture was stirred for 20 min at -78 °C. To the solution was added 1-(diphenylmethyl)azetidin-3-one (500 mg, 2.1 mmol), prepared using procedures similar to those described in Example 15. After stirring for 1 h, saturated aqueous ammonium chloride was added, and the mixture was warmed to rt. Water and ether were added, and the resulting biphasic mixture was partitioned. The aqueous phase was extracted once with ether. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (80% hexanes: 20% ethyl acetate) to provide 1,1-dimethylethyl [1-(diphenylmethyl)-3-hydroxyazetidin-3-yl]acetate as a pale yellow solid (644 mg, 1.8 mmol, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (m, 4H), 7.26 (m, 4H), 7.19 (m, 2H), 4.40 (s, 1H), 4.02 (s, 1H), 3.15 (m, 2H), 3.05 (m, 2H), 2.83 (s, 2H), 1.45 (s, 9H).

[00370] To a solution of 1,1-dimethylethyl [1-(diphenylmethyl)-3-hydroxyazetidin-3-yl]acetate (333 mg, 0.94 mmol) in THF (3 mL) at 0 °C was added lithium aluminum hydride (940 μL of a 1.0 M solution in THF, 0.94 mmol). The mixture was stirred for 3 h 20 min while warming to rt. Water (36 μL) was added carefully to the solution, followed by 15% sodium hydroxide (36 μL) and more water (108 μL). The resulting precipitate was removed by filtration through celite, and the filtrate was concentrated to dryness yielding 1-(diphenylmethyl)-3-(2-hydroxyethyl)azetidin-3-ol (228 mg, 0.80 mmol, 85% yield) as a colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (m, 4H), 7.26 (m, 4H), 7.19 (m, 2H), 4.37 (s, 1H), 3.92 (m, 2H), 3.32 (m, 2H), 2.96 (m, 2H), 2.07 (m, 2H).

[00371] Palladium hydroxide (100 mg) was suspended in a solution of 1-(diphenylmethyl)-3-(2-hydroxyethyl)azetidin-3-ol (228 mg, 0.80 mmol) in methanol (15 mL), and the mixture was subjected to an atmosphere of hydrogen at 50 psi for 4 h. The catalyst was then removed by filtration through celite, and the filtrate was concentrated *in vacuo* to provide 3-(2-hydroxyethyl)azetidin-3-ol. This material was used in the subsequent reaction without purification. To a solution of 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid (314 mg, 0.80 mmol), prepared using procedures similar to those described in US 7,019,033, in DMF (4 mL) was added PyBOP (416 mg, 0.80 mmol) and triethylamine (223 μL, 1.6 mmol). Finally, the unpurified 3-(2-hydroxyethyl)azetidin-3-ol was added, and the resulting mixture was stirred at rt for 16 h. Water and ethyl acetate were added, and the layers were separated. The aqueous phase was extracted with once more with ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography, eluting with ethyl acetate, to provide 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(2-hydroxyethyl)azetidin-3-ol as a colorless oil (303 mg, 0.62 mmol, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (s, 1H), 7.39 (dd, 1H), 7.32 (m, 1H), 7.13 (m, 1H), 6.81 (m, 1H), 6.60 (m, 1H), 4.37 (br s, 1H), 4.28 (br m, 4H), 3.94 (br s, 2H), 2.19 (br s, 1H), 2.02 (m, 2H); MS (EI) for $C_{18}H_{16}F_3IN_2O_3$: 491 (MH^+).

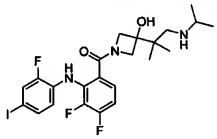
[00372] A solution of oxalyl chloride (13 μL, 0.15 mmol) in dichloromethane (1 mL) was cooled to -78 °C, and DMSO (22 μL, 0.31 mmol) was then added. To this mixture was added 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(2-hydroxyethyl)azetidin-3-ol (67.8 mg, 0.14 mmol) as a suspension in dichloromethane (1 mL). After stirring at -78 °C for 10 min, triethylamine (78 μL, 0.56 mmol) was added and the mixture was allowed to warm to rt. The solution was diluted with dichloromethane, and washed with 0.5 N HCl. The aqueous phase wash then extracted with dichloromethane. The organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography to provide [1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]acetaldehyde as a white solid (22.1 mg, 0.045 mmol, 32% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.82 (s, 1H), 8.46 (s, 1H), 7.39 (m, 1H), 7.33 (m, 1H), 7.11 (m, 1H), 6.81 (m, 1H),

6.61 (m, 1H), 4.32-3.96 (br m, 4H), 3.41 (t, 2H), 3.07 (s, 1H); MS (EI) for $C_{18}H_{14}F_3IN_2O_3$: 491 (MH^+).

[00373] To a solution of [1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]acetaldehyde (38.0 mg, 0.078 mmol) in 1,2-dichloroethane (1 mL) was added isopropylamine (27 μL, 0.31 mmol) followed by sodium triacetoxyborohydride (26 mg, 0.12 mmol). The mixture was stirred for 3 h before quenching with 1 drop of concentrated HCl. The quenched mixture was concentrated to dryness, and then purified by preparative HPLC to provide 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{2-[(1-methylethyl)amino]ethyl}azetidin-3-ol (21.5 mg) as a pale yellow solid. ^1H NMR (400 MHz, d_6-DMSO): δ 8.54 (s, 1H), 7.57 (dd, 1H), 7.38 (dd, 1H), 7.31 (m, 1H), 7.17 (m, 1H), 6.67 (m, 1H), 4.02 (m, 1H), 3.89 (m, 2H), 3.71 (m, 1H), 2.70 (m, 1H), 2.63 (m, 2H), 1.86 (s, 3H), 1.75 (m, 2H), 0.97 (d, 6H); MS (EI) for $C_{21}H_{23}F_3IN_3O_2$: 534 (MH^+).

EXAMPLE 18

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{1,1-dimethyl-2-[(1-methylethyl)amino]ethyl}azetidin-3-ol



[00374] To a solution of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-one (500 mg, 1.12 mmol), prepared using procedures similar to those described in Example 6, in dichloromethane (5 mL) cooled to 0 °C was added titanium tetrachloride (125 μL, 1.12 mmol). The dark brown solution was stirred at 0 °C for 45 minutes, followed by the addition of methyltrimethylsilyl dimethylketene acetal (550 μL, 2.24 mmol) at 0 °C. Upon addition the solution was allowed to warm to room temperature, and was stirred for 1 hour. The reaction mixture was then partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The aqueous portion was extracted twice using ethyl acetate. The combined organic portion was washed with water, brine, dried over

sodium sulfate, filtered and concentrated *in vacuo* to afford a brown oil which was purified by column chromatography. Eluting with 10% diethyl ether in dichloromethane, the isolated product was concentrated *in vacuo* to afford 520 mg, 0.95 mmol (85%) of methyl 2-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]-2-methylpropanoate as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): 8.34 (s, 1H), 7.38 (d, 1H), 7.31 (d, 1H), 7.13-7.08 (m, 1H), 6.85-6.77 (m, 1H), 6.63-6.56 (m, 1H), 4.26-4.20 (m, 2H), 4.13-4.09 (m, 1H), 4.00-3.93 (m, 1H), 3.70 (s, 3H), 1.23 (s, 6H). MS (EI) for $C_{21}H_{20}F_3IN_2O_4$: 547 (MH^+).

[00375] A solution of methyl 2-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]-2-methylpropanoate (520 mg, 0.95 mmol) in 4N aqueous potassium hydroxide (5 mL) was stirred at 50°C for 1 hour. Using concentrated aqueous hydrochloric acid, the reaction mixture was acidified to pH 5, and then partitioned with ethyl acetate. The aqueous portion was extracted twice using ethyl acetate, and the combined organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 300 mg, 0.56 mmol (59%) of 2-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]-2-methylpropanoic acid as a white solid. ^{1}H NMR (400 MHz, DMSO): 8.49 (s, 1H), 7.57-7.52 (m, 1H), 7.37-7.25 (m, 2H), 7.17-7.13 (m, 1H), 6.68-6.58 (m, 1H), 3.98-3.94 (m, 2H), 3.80-3.77 (m, 1H), 3.55-3.52 (m, 1H), 0.88 (s, 6H). MS (EI) for $C_{20}H_{18}F_3IN_2O_4$: 535 (MH^+).

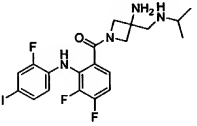
[00376] To solution of 2-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]-2-methylpropanoic acid (300 mg, 0.56 mmol) in tetrahydrofuran (5 mL) was added triethylamine (80 μL, 0.56 mmol), followed by PyBOP (295 mg, 0.56 mmol) and finally sodium borohydride (64 mg, 1.68 mmol). The mixture was stirred at room temperature for 1 hour. The reaction mixture was quenched by adding 20% aqueous citric acid, and then partitioned with ethyl acetate. The organic portion was washed with saturated aqueous sodium bicarbonate, brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a white solid which was purified by column chromatography. Eluting with 60% ethyl acetate in hexanes, the isolated product was concentrated *in vacuo* to afford 238 mg, 0.46 mmol (82%) of 1-({3,4-difluoro-2-[(2-

fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(2-hydroxy-1,1-dimethylethyl)azetidin-3-ol as a white solid. ^{1}H NMR (400 MHz, DMSO): 8.53 (s, 1H), 7.57 (d, 1H), 7.38-7.28 (m, 2H), 7.22-7.15 (m, 1H), 6.70-6.64 (m, 1H), 5.61 (s, 1H), 4.57 (br s, 1H), 4.30-4.27 (m, 1H), 4.18-4.15 (m, 1H), 3.80-3.77 (m, 1H), 3.68-3.64 (m, 1H), 3.25 (s, 2H), 0.76 (d, 6H); MS (EI) for $C_{20}H_{20}F_3IN_2O_3$: 521 (MH^+).

[00377] A mixture of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(2-hydroxy-1,1-dimethylethyl)azetidin-3-ol (200 mg, 0.38 mmol) and Dess-Martin periodinane (240 mg, 0.57 mmol) in dichloromethane (2 mL) was stirred at room temperature for 2 hours. 10% aqueous sodium thiosulfate (2 mL), and saturated aqueous sodium bicarbonate (2 mL) was added and the mixture was stirred at room temperature for 15 minute. The mixture was partitioned and the aqueous layer was extracted twice using dichloromethane. The combined organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*, to afford a white solid which was purified by column chromatography. Eluting with 30% ethyl acetate in hexanes, the isolated product was concentrated *in vacuo* to afford 100 mg, 0.20 mmol (53%) of 2-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]-2-methylpropanal as a white solid, which was immediately dissolved in tetrahydrofuran (2 mL). To the solution was added isopropylamine (34 µL, 0.40 mmol), followed by triacetoxyborohydride (212 mg, 1.0 mmol). The solution was stirred at room temperature for 15 hours. The reaction mixture was concentrated *in vacuo* and partitioned between 20% aqueous citric acid and ethyl acetate. The aqueous portion was extracted twice using ethyl acetate, and the combined organic portion was washed with saturated aqueous sodium bicarbonate, brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a yellow oil which was purified by preparative reverse phase HPLC. The isolated product was concentrated *in vacuo* to afford 50 mg, 0.07 mmol (36%) of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{1,1-dimethyl-2-[(1-methylethyl)amino]ethyl}azetidin-3-ol acetate salt as a white solid. ^{1}H NMR (400 MHz, DMSO): 8.47 (br s, 1H), 7.55 (d, 1H), 7.36-7.29 (m, 2H), 7.22-7.15 (m, 1H), 6.68-6.63 (m, 1H), 4.17-4.08 (m, 2H), 3.76-3.73 (m, 1H), 3.56-3.52 (m, 1H), 2.58-2.51 (m, 1H), 2.45-2.37 (m, 2H), 0.92 (t, 6H), 0.78 (d, 6H); MS (EI) for $C_{23}H_{27}F_3IN_3O_2$: 562 (MH^+).

EXAMPLE 19

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-methylethyl)amino]methyl}azetidin-3-amine



[00378] To a solution of the 1-(diphenylmethyl)-3-[(phenylmethyl)amino]azetidine-3-carbonitrile (0.80 g, 2.2 mmol), prepared using procedures similar to those described in Kozikowski and Fauq *Synlett* **1991,** *11,* 783-4, in ethanol (30 mL) was added solid sodium hydroxide (7.5 mmol), and the resulting mixture was stirred at room temperature for 3 days. Water (6 mL) was added to the reaction mixture and stirring was continued at 90 °C for 2 h. The pH of the reaction mixture was adjusted to 5 with concentrated hydrochloric acid and a white solid precipitated. The mixture was cooled , diluted with water (50 mL) and the solid was collected, washed with water then dried *in vacuo* to give the 1-(diphenylmethyl)-3-[(phenylmethyl)amino]azetidine-3-carboxylic acid (0.75g, 88% yield), MS (EI) for $C_{24}H_{24}N_2O_2$: 373 (MH^+).

[00379] To a mixture of 1-(diphenylmethyl)-3-[(phenylmethyl)amino]azetidine-3-carboxylic acid (0.50 g, 1.34 mmol), *N,N*-diisopropylethylamine (0.47 mL, 2.68 mmol) in DMF (3 mL) was added 1-benzotriazolyloxytripyrrolidinylphosphonium hexafluorophosphate (1.34g, 2.68 mol) and the resulting mixture was stirred at room temperature for 10 minutes. To this mixture was added 2-propylamine (0.22 mL, 2.68 mmol) and stirring was continued for 18 h. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with 2% aqueous citric acid, 5% lithium chloride, and brine solutions (50 mL each), dried over sodium sulfate, filtered and concentrated to give an oily residue which was purified by flash chromatography (silica gel, eluting with 15-25% ethyl acetate-hexane) to give 1-(diphenylmethyl)-*N*-(1-methylethyl)-3-[(phenylmethyl)amino]azetidine-3-carboxamide (0.51 g, 92% yield), MS (EI) for $C_{27}H_{31}N_3O$: 414 (MH^+).

[00380] To a solution of the 1-(diphenylmethyl)-*N*-(1-methylethyl)-3-[(phenylmethyl)amino]azetidine-3-carboxamide (0.40 g, 0.97 mmol) in tetrahydrofuran (10 mL) at room was added a solution of lithium aluminum hydride in tetrahydrofuran (1M, 2.90 mL, 2.90 mmol), and the resulting mixture was stirred at 50 °C for 3h. The reaction mixture was cooled to room temperature, quenched with 20% aqueous hydroxide solution (1 mL), diluted with ether (50 mL) and filtered. The filtrate was washed with brine solution (20 mL each), dried over sodium sulfate, filtered and concentrated to give an oily residue which was purified by flash chromatography (silica gel, eluting with 5% methanol-dichloromethane) to give 1-(diphenylmethyl)-3-{[(1-methylethyl)amino]methyl}-*N*-(phenylmethyl)azetidin-3-amine (0.35g, 90% yield), ^{1}H NMR (400 MHz, $CDCl_3$): 7.42-7.14 (m, 15H), 4.34 (s, 1H), 3.66 (s, 2H), 3.22-3.18 (d, 2H), 2.97 (s, 2H), 2.90-2.86(d, 2H), 2.68-2.62 (p, 1H), 1.09-1.07 (d, 6H); MS (EI) for $C_{27}H_{33}N_3$: 400 (MH^+).

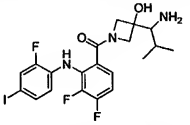
[00381] To a solution of the 1-(diphenylmethyl)-3-{[(1-methylethyl)amino]methyl}-*N*-(phenylmethyl)azetidin-3-amine (0.35 g , 0.88 mmol) in methanol was added a solution of hydrogen chloride in dioxane (4 molar solution, 0.96 mL, 4.40 mmol) and the resulting mixture was concentrated to give a white solid which was taken back into methanol. To this solution were added palladium hydroxide (20% on carbon, 0.50 g, 0.19 mmol) and the resulting mixture shaken at 50 psi in a Parr apparatus for 3h. The reaction mixture was filtered and concentrated to give a solid, which was washed with ether and dried *in vacuo* to give 3-{[(1-methylethyl)amino]methyl}azetidin-3-amine hydrochloride as a white solid (0.18 g, 81% yield). MS (EI) for $C_7H_{17}N_3$: 144 (MH^+).

[00382] To a mixture of the 3-{[(1-methylethyl)amino]methyl}azetidin-3-amine hydrochloride (20 mg, 0.079 mmol) in saturated sodium bicarbonate solution (1.0 mL) and dioxane (1.0 mL) was added 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoyl fluoride (31 mg, 0.079 mmol), prepared using procedures similar to those described in Reference 1, and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined extract was washed with water then brine solution (5 mL each), dried over sodium sulfate, filtered and concentrated to give an oily residue which was purified by reverse phase HPLC to afford 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-methylethyl)amino]methyl}azetidin-3-amine (15 mg, 37% yield). ^{1}H NMR (400

MHz, d_4-Methanol): 7.46-7.43 (dd, 1H), 7.35-7.33 (dd, 1H), 7.31-7.27 (m, 1H), 7.08-7.01 (dd, 1H), 6.63, 6.58 (td, 1H), 4.09-4.07 (d, 1H), 3.91-3.85 (dd, 2H), 3.76-3.73 (d, 1H). 2.80-2.74 (m, 1H), 2.73 (s, 2H), 1.07-1.05 (d, 6H); MS (EI) for $C_{20}H_{22}F_3IN_4O$: 519 (MH^+).

EXAMPLE 20

3-(1-amino-2-methylpropyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol



[00383] 1,1-Dimethylethyl 3-oxoazetidine-1-carboxylate (677.2 mg, 3.96 mmol), prepared using procedures similar to those described in Example 3, was taken into 2-methyl-1-ntropropane (5 mL) then cooled to 0 °C followed by addition of potassium *tert*-butoxide (444 mg, 3.96 mmol) and the resulting mixture was allowed to warm to room temperature over 30 minutes. The mixture was partitioned with ethyl acetate and 0.5 N aqueous hydrochloric acid then once with water and brine then dried over anhydrous magnesium sulfate. Filtration and concentration afforded a residue (1.5 g) that was further purified by silica gel flash chromatography using 3:1 hexanes:ethyl acetate as eluent to give 1,1-dimethylethyl 3-hydroxy-3-(2-methyl-1-nitropropyl)azetidine-1-carboxylate (730 mg, 67% yield) as a colorless crystalline solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.50 (d, 1H), 3.93 (dd AB, 2H), 3.85 (s, 2H), 3.58 (s, 1H), 2.54-2.48 (m, 1H), 1.44 (s, 9H), 1.04 (d, 6H).

[00384] 1,1-Dimethylethyl 3-hydroxy-3-(2-methyl-1-nitropropyl)azetidine-1-carboxylate (105 mg, 0.38 mmol) was taken into methanol (1 mL) followed by addition of 4 N anhydrous hydrogen chloride in dioxane (1 mL) and the acidic solution was allowed to stand for 15 minutes at room temperature then concentrated and dried *in vacuo* to an amorphous residue. 3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid (150 mg, 0.38 mmol), prepared using procedures similar to those described in US 7,019,033, was taken into DMF (0.7 mL) followed by addition of PyBOP (198 mg, 0.38 mmol) and the solution was allowed to stir for 10

minutes at room temperature. The above amine hydrochloride salt and DIPEA (190 μL, 1.1 mmol) in DMF solution (0.7 mL) was added and the mixture was allowed to stir for one hour at room temperature. The mixture was partitioned with ethyl acetate and 0.5 N aqueous hydrochloric acid and the organic phase washed three times with water then brine and dried over anhydrous magnesium sulfate. Filtration and concentration afforded a residue that was further purified by silica gel flash chromatography using 1.5:1 hexanes:ethyl acetate as eluent to give 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(2-methyl-1-nitropropyl)azetidin-3-ol (189 mg, 90% yield) as an amorphous solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.41 (br s, 1H), 7.41 (dd, 1H), 7.34 (d, 1H), 7.09 (br m, 1H), 6.81 (q, 1H), 6.65-6.60 (m, 1H), 4.49 (d, 1H), 4.15-4.09 (m, 4H), 3.66 (s, 1H), 2.56-2.46 (m, 1H) 1.03 (d, 6H).

[00385] 1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(2-methyl-1-nitropropyl)azetidin-3-ol (189 mg, 0.34 mmol) was taken into 4:1 THF:water (5 mL) followed by addition of iron powder (192 mg, 3.4 mmol) and ammonium formate (429 mg, 6.8 mmol) and the mixture was heated to reflux. After four hours additional aliquots of iron powder (192 mg, 3.4 mmol) and ammonium formate (429 mg, 6.8 mmol) were added and the mixture was allowed to reflux an additional 12 hours. The mixture was cooled to room temperature and diluted with ethyl acetate then filtered. The filtrate was partitioned with ethyl acetate and saturated aqueous sodium bicarbonate then the organic layer washed with brine and dried over anhydrous sodium sulfate. Filtration and concentration afforded a residue that was further purified by silica gel flash chromatography using ethyl acetate to 10% methanol in dichloromethane as eluents to give a residue (36.5 mg) that was further purified by preparative reverse phase HPLC to give 3-(1-amino-2-methylpropyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol trifluoroacetate salt (7.9 mg) as a colorless amorphous solid after lyophillization of the combined pure fractions. ^{1}H-NMR (400 MHz, D_6-DMSO): 8.63 (s, 1H), 7.58 (dd, 1H), 7.37 (d, 1H), 7.35-7.31 (m, 1H), 7.17 (q, 1H), 6.71-6.66 (m, 1H), 4.23 (dd, 1H), 4.03 (dd, 1H), 3.80 (dd, 1H), 3.66 (dd, 1H), 2.34 (dd, 1H), 1.79-1.70 (m, 1H), 0.84-0.77 (m, 6H). MS (EI) for $C_{20}H_{21}F_3IN_3O_2$: 520 (MH^+).

[00386] Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compounds of the invention were prepared:

EXAMPLE 20(a). 3-(1-aminoethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.56 (s, 1H), 7.91 (br s, 2H), 7.58 (d, 1H), 7.39 (d, 1H), 7.36-7.32 (m, 1H), 7.24-7.17 (m, 1H), 6.72-6.65 (m, 2H), 4.33-4.29 (m, 1H), 4.23-4.19 (m, 1H), 4.16-4.14 (m, 1H), 4.07-3.94 (m, 1H), 3.82-3.77 (m, 1H), 3.51-3.45 (m, 1H), 1.15-1.12 (m, 1H), 1.10-1.08 (m, 1H). MS (EI) for $C_{18}H_{17}F_3IN_3O_2$: 492 (MH^+).

EXAMPLE 20(b). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[1-(ethylamino)ethyl]azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.61 (d, 1H), 8.50 (s, 1H), 8.20 (s, 1H), 7.59 (d, 1H), 7.39 (d, 1H), 7.36-7.32 (m, 1H), 7.24-7.17 (m, 1H), 6.82 (s, 1H), 6.74-6.67 (m, 1H), 4.38 (d, 1H), 4.27 (d, 1H), 4.18 (d, 1H), 4.06 (d, 2H), 3.99 (d, 1H), 3.89 (d, 1H), 3.82 (d, 1H), 3.49-3.43 (m, 1H), 3.04-2.80 (m, 4H), 1.21-1.12 (m, 6H). MS (EI) for $C_{20}H_{21}F_3IN_3O_2$: 520 (MH^+).

EXAMPLE 20(c). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-nitroethyl)azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.57 (d, 1H), 7.58 (d, 1H), 7.38 (d, 1H), 7.37-7.33 (m, 1H), 7.22-7.17 (m, 1H), 6.73-6.66 (m, 1H), 6.57 (s, 1H), 5.06-4.97 (m, 1H), 4.54 (d, 0.5H), 4.37 (d, 0.5 H), 4.29 (d, 0.5H), 4.14 (d, 0.5 H), 4.05 (d, 0.5 H), 3.95 (d, 0.5H), 3.86 (d, 0.5H), 3.80 (d, 0.5H), 1.44-1.38 (m, 3H). MS (EI) for $C_{18}H_{16}F_3IN_3O_4$: 523 (MH^+).

EXAMPLE 20(d). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[1-(methylamino)ethyl]azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.63-8.55 (m, 1H), 8.44-8.23 (m, 1H), 7.79 (br s, 1H), 7.60 (d, 1H), 7.39 (d, 1H), 7.36-7.31 (m, 1H), 7.24-7.17 (m, 1H), 6.82 (br s, 0.5H), 6.73-6.65 (m, 1H), 4.38-3.77 (m, 4H), 1.18-1.07 (m, 3H). MS (EI) for $C_{19}H_{19}F_3IN_3O_2$: 505 (M^+).

EXAMPLE 20(e). methyl {1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}carbamate: ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 7.58 (d, 1H), 7.41-7.05 (m, 4H), 6.72-6.64 (m, 1H), 5.84 (d, 1H), 4.20 (d, 0.5H), 4.08-4.04 (m, 1H), 3.92-3.85 (m, 1.5H), 3.76-3.71 (m, 1H), 3.69-3.63 (m, 1H), 3.46 (d, 2H), 0.99-0.95 (m, 3H). MS (EI) for $C_{20}H_{19}F_3IN_3O_4$: 550 (MH^+).

EXAMPLE 20(f). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[1-(dimethylamino)ethyl]azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 9.45 (s, 1H), 8.61 (d, 1H), 7.60 (d, 1H), 7.39 (d, 1H), 7.38-7.33 (m, 1H), 7.24-7.18 (m, 1H), 7.05 (s, 1H), 6.73-6.66 (m, 1H), 4.48 (d, 0.5H), 4.36 (d, 0.5 H), 4.26 (d, 0.5H), 4.16-4.11 (m, 1H), 4.00-3.94 (m, 1H), 3.86 (d, 0.5H), 3.60-3.54 (m, 1H), 2.75-2.70 (m, 3H), 2.66-2.62 (br s, 3H), 1.22 (dd, 3H). MS (EI) for $C_{20}H_{21}F_3IN_3O_2$: 520 (MH^+).

EXAMPLE 20(g). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-nitropropyl)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.46 (m, 1H), 7.35 (m, 1H), 7.28 (m, 1H), 7.07 (m, 1H), 6.61 (m, 1H), 4.65 (m, 1H), 4.44 (m, 1H), 4.25 (m, 1H), 4.02 (m, 1H), 3.86 (m, 1H), 2.04 (m, 1H), 1.76 (m, 1H), 0.94 (m, 3H). MS (EI) for $C_{19}H_{17}F_3IN_3O_4$: 536 (MH^+).

EXAMPLE 20(h). 3-(1-aminopropyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.45 (m, 1H), 7.34 (m, 1H), 7.28 (m, 1H), 7.05 (m, 1H), 6.61 (m, 1H), 4.21 (m, 1H), 4.09-3.86 (m, 2H), 3.78 (m, 1H), 2.63 (m, 1H), 1.50 (m, 1H), 1.24 (m, 1H), 0.98 (m, 3H). MS (EI) for $C_{19}H_{19}F_3IN_3O_2$: 506 (MH^+).

EXAMPLE 20(i). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[1-(ethylamino)propyl]azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.45 (m, 1H), 7.34 (m, 1H), 7.28 (m, 1H), 7.05 (m, 1H), 6.61 (m, 1H), 4.23 (m, 1H), 4.02 (m, 1H), 3.90 (m, 1H), 3.79 (m, 1H), 2.70 (m, 1H), 2.54 (m, 1H), 1.53 (m, 1H), 1.40 (m, 1H), 1.05 (m, 3H), 0.95 (m, 3H). MS (EI) for $C_{21}H_{23}F_3IN_3O_2$: 534 (MH^+).

EXAMPLE 20(j). 3-[1-(diethylamino)propyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.44 (m, 1H), 7.33 (m, 1H), 7.27 (m, 1H), 7.07 (m, 1H), 6.60 (m, 1H), 4.21 (m, 1H), 4.10 (m, 1H), 4.03-3.70 (m, 2H), 2.71-2.45 (m, 5H), 1.67 (m, 1H), 1.49 (m, 1H), 0.94 (m, 9H). MS (EI) for $C_{23}H_{27}F_3IN_3O_2$: 562 (MH^+).

EXAMPLE 20(k). 3-[amino(phenyl)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol): MS (EI) for $C_{23}H_{19}F_3IN_3O_2$: 554 (MH^+).

EXAMPLE 20(m). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(3-methyl-1-nitrobutyl)azetidin-3-ol): ^{1}H NMR (400MHz, $CDCl_3$): 8.38 (s, 1H), 7.39 (dd, 1H), 7.34-7.31 (m, 1H), 7.14-7.10

(m, 1H), 6.84-6.77 (m, 1H), 6.63-6.58 (m, 1H), 4.68 (dd, 1H), 4.23-4.04 (br m, 4H), 2.13 (t, 2H), 1.64-1.44 (br m, 3H), 0.93 (d, 6H); MS (EI) for $C_{21}H_{21}F_3IN_3O_4$: 564 (MH^+).

EXAMPLE 20(n). 3-(1-aminobutyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^1H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.38-7.33 (d, 1H), 7.32-7.26 (m, 1H), 7.09-7.00 (q, 1H), 6.66-6.58 (t, 1H), 4.33-4.22 (d, 1H), 4.13-3.81 (m, 3H), 3.17-3.09 (t, 1H), 1.93-1.89 (s, 3H), 1.89-1.82 (t, 3H), 1.56-1.24 (m, 4H), 0.97-0.88 (t, 3H); MS (EI) for $C_{20}H_{21}F_3IN_3O_2$: 520 (MH^+).

EXAMPLE 20(o). 3-(1-aminocyclopentyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^1H NMR (400 MHz, $CDCl_3$): 8.27-8.21 (s, 1H), 7.42-7.36 (d, 1H), 7.34-7.29 (d, 1H), 7.15-7.09 (t, 1H), 7.09-7.01 (q, 1H), 6.88-6.79 (q, 1H), 6.63-6.53 (m, 1H), 4.18-3.92 (m, 4H), 2.12-2.08 (s, 3H), 2.06-1.70 (m, 7H), 0.92-0.68 (m, 4H); MS (EI) for $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+).

EXAMPLE 20(p). *N*-{1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}acetamide: ^1H NMR (400 MHz, CDCl3): 8.42 (s, 1H), 7.41-7.38 (dd, 1H), 7.34-7.32 (dt, 1H), 7.12-7.09 (m, 1H), 6.85-6.78 (m, 1H), 6.63-6.57 (m, 1H), 5.76 (b, 1H), 4.28-3.98 (m, 5H), 2.00 (s, 3H), 1.20-1.19 (d, 3H); MS (EI) for $C_{20}H_{19}F_3IN_3O_3$: 534 (MH^+).

EXAMPLE 20(q). (2R)-*N*-{1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanamide: ^1H NMR (400 MHz, CDCl3): 8.47 (s, 1H), 7.45-7.40 (m, 5H), 7.33-7.31 (m, 1H), 7.21-7.19 (m, 1H), 7.12-7.05 (m, 1H), 6.85-6.76 (m, 1H), 6.63-6.58 (m, 1H), 4.20-3.99 (m, 5H), 3.36 (s, 1.5H), 3.34 (s,1.5H), 1.27-1.25 (d, 1.5H), 1.24-1.22 (d, 1.5H); MS (EI) for $C_{28}H_{24}F_6IN_3O_4$: 708 (MH^+).

EXAMPLE 20(r). (2R)-*N*-{(1R)-1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanamide: ^1H NMR (400 MHz, CDCl3): 8.49 (s, 1H), 7.46-7.391 (m, 5H), 7.33-7.31 (m, 1H), 7.21-7.16 (m, 1H), 7.14-7.10 (m, 1H), 6.85-6.79 (m, 1H), 6.64-6.58 (m, 1H), 4.24-4.00 (m, 5H), 3.35 (s, 3H), 1.25-1.23 (d, 3H); MS (EI) for $C_{28}H_{24}F_6IN_3O_4$: 708 (MH^+).

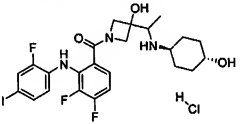
EXAMPLE 20(s). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-methyl-1-nitroethyl)azetidin-3-ol: ^1H

NMR (400 MHz, CDCl3): 8.28 (s, 1H), 7.41-7.38 (dd, 1H), 7.34-7.32 (dt, 1H), 7.14-7.10 (m, 1H), 6.87-6.81 (m, 1H), 6.64-6.59 (m, 1H), 4.33-4.15 (m, 4H), 1.64 (s, 6H); MS (EI) for $C_{19}H_{17}F_3IN_3O_4$: 536 (MH^+).

EXAMPLE 20(t). 3-(1-amino-1-methylethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400 MHz, CDCl3): 8.30 (s, 1H), 7.39-7.36 (dd, 1H), 7.32-7.30 (dt, 1H), 7.13-7.09 (m, 1H), 6.85-6.79 (m, 1H), 6.62-6.56 (m, 1H), 4.25-3.97 (m, 4H), 1.14 (s, 6H); MS (EI) for $C_{19}H_{19}F_3IN_3O_2$: 506 (MH^+).

EXAMPLE 21

1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{1-[(*trans*-4-hydroxycyclohexyl)amino]ethyl}azetidin-3-ol hydrochloride



[00387] Potassium *tert*-butoxide (1.672 g, 14.9 mmol) and ethyltriphenylphosphonium bromide (5.538 g, 14.9 mmol) were stirred in ether (30 mL) at amibient for 1 h. 1,1-Dimethylethyl 3-oxoazetidine-1-carboxylate (954 mg, 6.0 mmol), prepared using procedures similar to those described in Example 3, was added and the mixture was 35 °C for 4.5 h. Mixture was filtered through celite and the solid was washed with ether. The filtrate was washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 20% ether in hexanes) gave 1,1-dimethylethyl 3-ethylideneazetidine-1-carboxylate (506 mg, 2.76 mmol, 49% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 5.37-5.28 (m, 1H), 4.47-4.39 (m, 4H), 1.56-1.51 (m, 3H), 1.45 (s, 9H).

[00388] 1,1-Dimethylethyl 3-ethylideneazetidine-1-carboxylate (506 mg, 2.76 mmol), and 4-methylmorpholine *N*-oxide (1.04 g, 8.89 mmol) were dissolved in acetone / water (4:1; 30 mL) and osmium tetroxide (2.5 wt.% in *t*-butanol; 0.2 mL) was added. The solution was stirred at ambient for 5 days, then was quenched with saturated sodium bisulfite (2 mL) and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and brine. The aqueous portion was extracted with

ethyl acetate. The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, ethyl acetate) gave 1,1-dimethylethyl 3-hydroxy-3-(1-hydroxyethyl)azetidine-1-carboxylate (375 mg, 1.73 mmol, 63% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 4.00-3.77 (m, 5H), 2.65 (br s, 1H), 1.86, (br s, 1H), 1.44 (s, 9H), 1.25 (d, 3H).

[00389] 1,1-Dimethylethyl 3-hydroxy-3-(1-hydroxyethyl)azetidine-1-carboxylate (200 mg, 0.922 mmol) was dissolved in methanol (5 mL) and 4 N hydrochloric acid in dioxane (1 mL, 4 mmol) was added. The mixture was refluxed for 15 minutes and then was concentrated *in vacuo* to afford 3-(1-hydroxyethyl)azetidin-3-ol hydrochloride (0.922 mmol).

[00390] 3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid (362 mg, 0.921 mmol), prepared using procedures similar to those described in US 7,019,033, 4-(dimethylamino)pyridine (337 mg, 2.76 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (212 mg, 1.11 mmol) were dissolved in DMF (3 mL). The mixture was stirred at ambient for 5 minutes and then 3-(1-hydroxyethyl)azetidin-3-ol hydrochloride (0.922 mmol) in DMF (2 mL) was added and the mixture was stirred for 15 h. The mixture was partitioned between ethyl acetate and 5% lithium chloride. The organic portion was washed with 20% citric acid, saturated sodium bicarbonate and brine, then was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 80% ethyl acetate in hexanes) gave 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-hydroxyethyl)azetidin-3-ol (296 mg, 0.602 mmol, 65% yield): MS (EI) for $C_{18}H_{16}F_3IN_2O_3$: 493 (MH^+).

[00391] 1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-hydroxyethyl)azetidin-3-ol (267 mg, 0.543 mmol), was dissolved in dichloromethane (10 mL) and treated with 4-(dimethylamino)pyridine (80 mg, 0.661 mmol) and 2,4,6-triisopropylbenzenesulfonyl chloride (183 mg, 0.604 mmol) at ambient for 15 h. Triethylamine (0.076 mL, 0.545 mmol) was added and the mixture was stirred at ambient for 3 h and then at 35 °C for 4 h and then at ambient for a furhter 15 h. 2,4,6-Triisopropylbenzenesulfonyl chloride (110 mg, 0.363 mmol) was added and the mixture was stirred at 35 °C for 3 h and then 4-(dimethylamino)pyridine (80 mg, 0.661 mmol) was added and the mixture was stirred at 35 °C for 2 h. 2,4,6-Triisopropylbenzenesulfonyl chloride (303 mg, 1.0 mmol) was

added and the mixture was stirred at 35 °C for a furhter 18 h. The mixture was adsorbed on to silica and purified by column chromatography (silica gel, 30-50% ethyl acetate in hexanes) to give 1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl 2,4,6-tris(1-methylethyl)benzenesulfonate (201 mg, 0.265 mmol, 49% yield): MS (EI) for $C_{33}H_{38}F_3IN_2O_5S$: 759 (MH^+).

[00392] 1-[1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl 2,4,6-tris(1-methylethyl)benzenesulfonate (194 mg, 0.256 mmol) was dissolved in tetrahydrofuran (2 mL) and was cooled to 0 °C. Sodium hydride (60 wt% dispersion in oil; 31 mg, 0.775 mmol) was added and the mixture was stirred at 0 °C for 15 minutes. The mixture was quenched with saturated sodium bicarbonate solution and partitioned with ethyl acetate. The aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 50% ethyl acetate in hexanes) gave 2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)-6-[(2-methyl-1-oxa-5-azaspiro[2.3]hex-5-yl)carbonyl]aniline (120 mg, 0.253 mmol, 99% yield): MS (EI) for $C_{18}H_{14}F_3IN_2O_2$: 475 (MH^+).

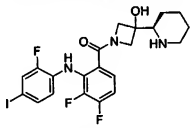
[00393] 2,3-Difluoro-*N*-(2-fluoro-4-iodophenyl)-6-[(2-methyl-1-oxa-5-azaspiro[2.3]hex-5-yl)carbonyl]aniline (50 mg, 0.105 mmol) was dissolved in dimethylsulfoxide (0.8 mL) and treated with *trans*-4-cyclohexanolamine (70 mg, 0.609 mmol) with 100 W microwave power at 100 °C for 45 minutes. The mixture was purified by reverse phase HPLC and the clean fractions were combined, neutralized with saturated sodium bicarbonate solution and the organic solvent was removed *in vacuo*. The remaining aqueous residue was extracted twice with ethyl acetate. The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give a residue which was treated with aqueous hydrochloric acid and then was lyophilized to afford 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{1-[(*trans*-4-hydroxycyclohexyl)amino]ethyl}azetidin-3-ol hydrochloride (36 mg, 0.058 mmol, 55% yield): ^1H NMR (400 MHz, d_6-DMSO): 8.61 (br s, 0.5H), 8.55 (br s, 0.5H), 8.49-8.33 (m, 1H), 8.08-7.90 (m, 1H), 7.59 (dd, 1H), 7.39 (br d, 1H), 7.37-7.30 (m, 1H), 7.21 (br q, 1H), 6.81 (br d, 1H), 6.77-6.65 (m, 1H), 4.20 (br d, 1H), 4.09-4.02 (m, 1H), 3.97 (br d, 1H), 3.93-3.80 (m, 1H), 3.62-3.47 (m, 1H), 3.03-2.90 (m, 1H),

2.07-1.93 (m, 2H), 1.93-1.77 (m, 2H), 1.54-1.06 (m, 8H); MS (EI) for $C_{24}H_{27}F_3IN_3O_3$: 590 (MH^+).

[00394] **EXAMPLE 21(a).** Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compound of the invention was prepared: 1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{1-[(1,1-dimethylethyl)amino]ethyl}azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.63 (br s, 0.4H), 8.53 (br s, 0.6H), 7.56 (dt, 1H), 7.40-7.34 (m, 1H), 7.32-7.26 (m, 1H), 7.25-7.13 (m, 1H), 6.72-6.62 (m, 1H), 5.43 (br s, 1H), 4.14-3.56 (m, 4H), 2.69-2.53 (m, 1H), 1.00-0.85 (br, 12H); MS (EI) for $C_{22}H_{25}F_3IN_3O_2$: 548 (MH^+).

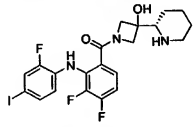
EXAMPLE 22(a) and 22(b)

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2R)-piperidin-2-yl]azetidin-3-ol



and

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2S)-piperidin-2-yl]azetidin-3-ol



[00395] To a solution of 1,1-dimethylethyl 2-(3-hydroxy-1-{[(phenylmethyl)oxy]carbonyl}azetidin-3-yl)piperidine-1-carboxylate (368 mg, 0.94 mmol), prepared using procedures similar to those described in Reference 5, in dichloromethane (5 mL) was added DMAP (115 mg, 0.94 mmol) and the resulting solution was cooled to 0°C. (*R*)-(-)-α-Methoxy-α-trifluoromethylphenylacetyl chloride (105 μL, 0.56 mmol) was added to the solution by syringe and the mixture

was allowed to warm to room temperature then stirred an additional 12 hours. The solution was then partitioned with saturated aqueous soldium bicarbonate and the organic phase dried over anhydrous magnesium sulfate then filtered and concentrated to an oily residue. Silica gel flash chromatography using hexanes:ethyl acetate 3:1 as eluent afforded the less polar 1,1-dimethylethyl (2*R*)-2-(1-{[(phenylmethyl)oxy]carbonyl}-3-{[(2*R*)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoyl]oxy}azetidin-3-yl)piperidine-1-carboxylate (27.5 mg, 5% yield), the more polar 1,1-dimethylethyl (2*S*)-2-(1-{[(phenylmethyl)oxy]carbonyl}-3-{[(2*R*)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoyl]oxy}azetidin-3-yl)piperidine-1-carboxylate (105 mg, 19% yield) and starting material (253 mg, 69% recovery).

[00396] The starting material thus recovered was taken into dichloromethane (3 mL) followed by addition of DMAP (115 mg, 0.94 mmol) and (*R*)-(-)-α-methoxy-α-trifluoromethylphenylacetyl chloride (105 μL, 0.56 mmol) and the mixture was allowed to stir at room temperature over 12 hours. Proceeding as before afforded combined 1,1-dimethylethyl (2R)-2-(1-{[(phenylmethyl)oxy]carbonyl}-3-{[(2*R*)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoyl]oxy}azetidin-3-yl)piperidine-1-carboxylate (46.6 mg, 8% yield), the more polar 1,1-dimethylethyl (2*S*)-2-(1-{[(phenylmethyl)oxy]carbonyl}-3-{[(2*R*)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoyl]oxy}azetidin-3-yl)piperidine-1-carboxylate (228 mg, 41% yield) and starting material (100.8 mg, 27% recovery).

[00397] The starting material thus recovered was taken into tetrahydrofuran:dichloromethane (1:1, 2 mL) followed by addition of DMAP (47 mg, 0.39 mmol) and (R)-(-)-α-methoxy-α-trifluoromethylphenylacetyl chloride (80 μL, 0.43 mmol) and the mixture was heated to 60 °C over 12 hours. Proceeding as before afforded combined less polar 1,1-dimethylethyl (2*R*)-2-(1-{[(phenylmethyl)oxy]carbonyl}-3-{[(2*R*)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoyl]oxy}azetidin-3-yl)piperidine-1-carboxylate (144 mg, 26 % yield). The chiral ester derivatives thus obtained were again subject to silica gel flash chromatography using hexanes:ethyl acetate 3:1 as eluent to give the pure less polar 1,1-dimethylethyl (2*R*)-2-(1-{[(phenylmethyl)oxy]carbonyl}-3-{[(2*R*)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoyl]oxy}azetidin-3-yl)piperidine-1-carboxylate (122.8 mg, 22% yield) and the more polar 1,1-dimethylethyl (2*S*)-2-(1-{[(phenylmethyl)oxy]carbonyl}-3-{[(2*R*)-3,3,3-trifluoro-2-(methyloxy)-2-

phenylpropanoyl]oxy}azetidin-3-yl)piperidine-1-carboxylate (177.6 mg, 32% yield) both as colorless amorphous residues.

[00398] 1,1-Dimethylethyl (2*R*)-2-(1-{[(phenylmethyl)oxy]carbonyl}-3-{[(2*R*)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoyl]oxy}azetidin-3-yl)piperidine-1-carboxylate (122.8 mg, 0.21 mmol) was taken into methanol (4 mL) followed by addition of 1M aqueous sodium hydroxide (1 mL) and the resulting solution was stirred for one hour at room temperature. The solution was then partitioned with ethyl acetate and 1N aqueous hydrochloric acid. The organic layer was washed with brine, dried over anhydrous magnesium sulfate then filtered and concentrated. The residue was purified by silica gel flash chromatography using hexanes:ethyl acetate 2:1 to give 1,1-dimethylethyl (2*R*)-2-(3-hydroxy-1-{[(phenylmethyl)oxy]carbonyl}azetidin-3-yl)piperidine-1-carboxylate (60.8 mg, 81% yield) a colorless amorphous solid. 1,1-dimethylethyl (2*S*)-2-(3-hydroxy-1-{[(phenylmethyl)oxy]carbonyl}azetidin-3-yl)piperidine-1-carboxylate (87.4 mg, 75% yield) was prepared analogously.

[00399] 1,1-Dimethylethyl (2*R*)-2-(3-hydroxy-1-{[(phenylmethyl)oxy]carbonyl}azetidin-3-yl)piperidine-1-carboxylate (60.8 mg, 0.16 mmol) and 10% Pd/C (30 mg) were taken into methanol (2 mL) and the mixture hydrogenated at ambient pressure for one hour. The suspension was then filtered through a celite pad and concentrated then dried *in vacuo* to a colorless solid. The solid amine was taken into THF (1 mL) followed by addition of DIPEA (42 μL, 0.24 mmol) and 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoyl fluoride (63 mg, 0.16 mmol), prepared using procedures similar to those described in Reference 1, and the mixture stirred at room temperature for 30 minutes. The reaction mixture was partitioned with ethyl acetate and 1 N aqueous hydrochloric acid and the organic layer washed with brine, dried over anhydrous magnesium sulfate then filtered and concentrated. Purification of the residue by silica gel flash chromatography using hexanes:ethyl acetate 3:2 as eluent afforded 1,1-dimethylethyl (2*R*)-2-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate (74.9 mg, 74% yield) as an amorphous solid. 1,1-Dimethylethyl (2*R*)-2-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate ^{1}H NMR (400 MHz, $CDCl_3$): 8.53 (br s, 0.5H), 8.40 (br s, 0.5H), 7.41-7.38 (dd, 1H), 7.34-7.31(dt, 1H), 7.17-7.14 (m, 1H), 6.86-6.79 (m, 1H), 6.63-6.587 (m, 1H), 4.24-

3.90 (m, 4H), 3.37-3.23 (m, 1H), 2.90-2.80 (m, 1H), 1.85-1.54 (m, 7H), 1.43 (s, 9H); MS (EI) for $C_{26}H_{29}F_3IN_3O_4$: 576 ($M-C_4H_9^+$).

[00400] 1,1-dimethylethyl (2*R*)-2-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate (74.9 mg, 0.12 mmol) was taken into methanol (1 mL) followed by addition of 4 N HCl in dioxane (1 mL) and the solution was stirred at room temperature for one hour. The solution was then concentrated and the residue partitioned with chloroform and saturated aqueous sodium bicarbonate. The organic layer was washed with brine, dried over anhydrous sodium sulfate then filtered and concentrated. Purification of the residue by silica gel flash chromatography using ethyl acetate then concentrated aqueous ammonia in chloroform and methanol (0.1:10:1) as eluents afforded 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2*R*)-piperidin-2-yl]azetidin-3-ol (57.3 mg) as a colorless amorphous solid. The free base was taken into methanol (1 mL) then brought to about pH 1 by addition of 4 N HCl in dioxane and the solution concentrated. The residue was triturated with ethyl ether to afford a suspension. The solid was collected by filtration to afford 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2*R*)-piperidin-2-yl]azetidin-3-ol hydrochloride salt (49 mg, 72% yield) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): 8.43-8.39 (d, 1H), 7.41-7.38 (dd, 1H), 7.33-7.31(dt, 1H), 7.14-7.10 (m, 1H), 6.84-6.80 (m, 1H), 6.63-6.57 (m, 1H), 4.12-3.99 (m, 4H), 3.10-3.08 (d, 1H), 2.72-2.69 (d, 1H), 2.64-2.62 (m, 1H), 1.61-1.58 (m, 2H), 1.36-1.16 (m, 4H); MS (EI) for $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+).

[00401] Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compounds of the invention were prepared:

EXAMPLE 22(c). 1,1-dimethylethyl (2S)-2-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate: ^{1}H NMR (400 MHz, $CDCl_3$): 8.52 (br s, 0.5H), 8.39 (br s, 0.5H), 7.41-7.38 (dd, 1H), 7.34-7.31(dt, 1H), 7.17-7.12 (m, 1H), 6.85-6.79 (m, 1H), 6.63-6.57 (m, 1H), 4.25-3.88 (m, 4H), 3.34-3.26 (m, 1H), 2.80-2.90 (m, 1H), 1.85-1.54 (m, 7H), 1.43 (s, 9H); MS (EI) for $C_{26}H_{29}F_3IN_3O_4$: 576 ($M-C_4H_9^+$).

EXAMPLE 22(d). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2S)-piperidin-2-yl]azetidin-3-ol hydrochloride: ^{1}H NMR (400 MHz, d_4-Methanol): 7.49-7.46 (dd, 1H), 7.37-7.35(dt,

1H), 7.35-7.30 (m, 1H), 7.10-7.04 (m, 1H), 6.64-6.59 (m, 1H), 4.39-4.32 (dd, 1H), 4.21-4.18 (dd, 1H), 4.13-4.07 (m, 1H), 3.97-3.88 (dd, 1H), 3.57-3.32 (m, 1H), 3.02-2.96 (dd,1H), 1.90-1.50 (m, 7H); MS (EI) for $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+).

EXAMPLE 22(e). 1-({2-[(4-bromo-2-chlorophenyl)amino]-3,4-difluorophenyl}carbonyl)-3-piperidin-2-ylazetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.56 (d, 1H), 7.29-7.38 (m, 2H), 7.08-7.16 (m, 1H), 6.64-6.70 (m, 1H), 4.30-4.40 (m, 1H), 4.18-4.26 (m, 1H), 4.04-4.14 (m, 1H), 3.90-4.00 (m, 1H), 3.16-3.26 (m, 2H), 2.86-2.96 (m, 1H), 1.91 (s, 3H), 1.76-1.88 (m, 3H), 1.44-1.64 (m, 3H). MS (EI) for $C_{21}H_{21}BrClF_2N_3O_2$: 500 (M-H).

EXAMPLE 22(f). 1-({2-[(4-bromo-2-fluorophenyl)amino]-3,4-difluorophenyl}carbonyl)-3-piperidin-2-ylazetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.52 (br s, 1H), 7.50 (d, 1H), 7.35-7.15 (m, 3H), 6.88-6.79 (m, 1H), 4.15-3.96 (m, 1H), 3.84-3.78 (m, 1H), 3.68-3.63 (m, 1H), 2.95-2.88 (m, 1H), 2.48-2.40 (m, 2H), 1.71-1.42 (m, 3H), 1.25-1.14 (m, 2H), 1.03-0.90 (m, 1H); MS (EI) for $C_{21}H_{21}BrF_3N_3O_2$: 485 (MH^+).

EXAMPLE 22(g). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-pyrrolidin-2-ylazetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.45 (dd, 1H), 7.37-7.31 (m, 1H), 7.30-7.25 (m, 1H), 7.13-6.99 (m, 1H), 6.67-6.54 (m, 1H), 4.20-4.09 (m,1H), 4.08-3.91 (m, 2H), 3.88-3.79 (m, 1H), 3.27 (t, 1H), 2.99-2.89 (m, 1H), 2.88-2.81 (m, 1H), 1.93-1.67 (m, 3H), 1.55-1.42 (m, 1H). MS (EI) for $C_{20}H_{19}F_3IN_3O_2$: 518 (MH^+)

EXAMPLE 22(h). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-methylpyrrolidin-2-yl)azetidin-3-ol acetate (salt): ^{1}H NMR (400 MHz, CD_3OD): 7.46 (dd, 1H), 7.38-7.26 (m, 2H), 7.12-6.99 (m, 1H), 6.66-6.56 (m, 1H), 4.37-3.87 (m,4H), 2.94-2.82 (m, 1H), 2.75-2.63 (m, 3H), 2.20-2.06 (m, 1H), 2.00-1.67 (m, 8H). MS (EI) for $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+).

EXAMPLE 22(i). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-ethylpyrrolidin-2-yl)azetidin-3-ol acetate (salt): ^{1}H NMR (400 MHz, CD_3OD): 7.46 (d, 1H), 7.38-7.33 (m, 1H), 7.32-7.27 (m, 1H), 7.12-7.01 (m, 1H), 6.66-6.57 (m, 1H), 4.34-3.89 (m,4H), 3.57 (t, 1H), 3.51-3.40 (m, 1H), 3.28-2.81(m, 3H), 2.25-1.72 (m, 8H), 1.31-1.18 (m, 3H). MS (EI) for $C_{22}H_{23}F_3IN_3O_2$: 546 (MH^+).

EXAMPLE 22(j). 1-({4-fluoro-5-[(2-fluoro-4-iodophenyl)amino]-1-methyl-1*H*-benzimidazol-6-yl}carbonyl)-3-[(2S)-piperidin-2-yl]azetidin-3-ol acetate salt: ^{1}H

NMR (400 MHz, d_4-MeOH): 8.30 (s, 1H), 7.56 (s, 1H), 7.42 (d, 1H), 7.24 (d, 1H), 6.34 (m, 1H), 4.20 (d, 2H), 3.92 (s, 3H), 3.38-3.24 (m, 3H), 3.08 (bs, 1H), 2.88 (bs (1*H*), 1.90-1.70 (m, 3H), 1.66-1.32 (m, 3H); MS (EI) for $C_{23}H_{24}F_2IN_5O_2$: 568 (MH^+).

EXAMPLE 22(k). 1-({7-fluoro-6-[(2-fluoro-4-iodophenyl)amino]-1-methyl-1*H*-benzimidazol-5-yl}carbonyl)-3-[(2S)-piperidin-2-yl]azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, d_4-MeOH): 8.22 (s, 1H), 7.60 (s, 1H), 7.42 (d, 1H), 7.26 (d, 1H), 6.46 (m, 1H), 4.21 (d, 2H), 4.06 (s, 3H), 3.88 (m, 1H), 3.38-3.24 (m, 3H), 3.10 (bs, 1H), 2.88 (bs (1*H*), 1.88-1.70 (m, 3H), 1.64-1.28 (m, 3H); MS (EI) for $C_{23}H_{24}F_2IN_5O_2$: 568 (MH^+).

EXAMPLE 22(m). 4-[(4-bromo-2-fluorophenyl)amino]-3-fluoro-5-({3-hydroxy-3-[(2S)-piperidin-2-yl]azetidin-1-yl}carbonyl)-1-methylpyridin-2(1*H*)-one: MS (EI) for $C_{21}H_{23}BrF_2N_4O_3$: 498 (MH^+).

EXAMPLE 22(n). 1-({8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-a]pyridin-6-yl}carbonyl)-3-[(2S)-piperidin-2-yl]azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.79 (s, 1H), 8.04 (d, 1H), 7.91 (d, 1H), 7.64 (dd, 1H), 7.55 (d, 1H), 6.95-7.02 (m, 1H), 4.38 (d, 1H), 4.15 (dd, 1H), 3.99 (dd, 1H), 3.72 (q, 1H), 3.32-3.39 (m, 1H), 3.00-3.12 (m, 1H), 1.93 (t, 3H), 1.51-1.70 (m, 3H); MS (EI) for $C_{22}H_{22}ClFIN_5O_2$: 532 (MH^+).

EXAMPLE 22(o). 1-({7-[(4-bromo-2-chlorophenyl)amino]-8-chloroimidazo[1,2-a]pyridin-6-yl}carbonyl)-3-[(2S)-piperidin-2-yl]azetidin-3-ol: ^{1}H NMR (400MHz, d_4-MeOH): 8.85 (s, 1H), 8.06 (d, 1H), 7.91 (d, 1H), 7.71 (d, 1H), 7.45 (d, 1H), 7.01 (d, 1H), 4.48 (d, 1H), 4.10-4.27 (m, 2H), 3.87 (q, 1H), 3.37 (d, 2H), 3.02 (s, 1H), 1.88-1.94 (m, 3H), 1.58-1.69 (m, 3H); $C_{22}H_{22}BrCl_2N_5O_2$: 540 (MH^+).

EXAMPLE 22(p). 1-({6-[(4-bromo-2-chlorophenyl)amino]-7-fluoro-3-methyl-1,2-benzisoxazol-5-yl}carbonyl)-3-[(2S)-piperidin-2-yl]azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.50 (m, 1H), 7.51 (d, 1H), 7.42 (s, 1H), 7.26 (dd, 1H), 6.79 (dd, 1H), 4.20-3.98 (br m, 4H), 3.11 (d , 1H), 2.77-2.50 (br m, 5H), 1.80-1.15 (br m, 6H); MS (EI) for $C_{23}H_{23}BrClFN_4O_3$: 537 (MH^+).

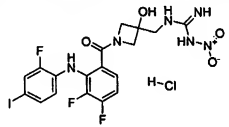
EXAMPLE 22(q). 1-({3-fluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2S)-piperidin-2-yl]azetidin-3-ol: ^{1}H NMR (400 MHz, d_4-MeOH): 7.53 (2d, 1H), 7.46 (m, 2H), 7.16 (t, 1H), 6.86 (m, 1H), 6.63 (m, 1H), 4.36 (m, 1H), 4.22 (m, 1H), 4.02 (m, 1H), 3.88 (m, 1H), 3.08 (d, 1H), 2.66 (dd, 1H), 2.56 (m, 1H), 1.82 (bs, 1H), 1.66 (d, 1H), 1.58 (d, 1H), 1.38 (m, 2H), 1.22 (m, 1H); MS (EI) for $C_{21}H_{22}F_2IN_3O_2$: 514 (MH^+).

EXAMPLE 22(r). 1-({4-fluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2S)-piperidin-2-yl]azetidin-3-ol: ^{1}H NMR (400 MHz, d_4-MeOH): 7.42 (2d, 1H), 7.34-7.18 (m, 4H), 6.46 (m, 1H), 4.10 (m, 2H), 3.84 (m, 2H), 3.04 (d, 1H), 2.52 (dd, 2H), 1.76 (bs, 0.5H), 1.58 (m, 2.5H), 1.32 (m, 2H), 1.18 (m, 0.5H), 1.04 (m, 0.5H); MS (EI) for $C_{21}H_{22}F_2IN_3O_2$: 514 (MH^+).

EXAMPLE 22(s). 5-[(2-fluoro-4-iodophenyl)amino]-6-({3-hydroxy-3-[(2S)-piperidin-2-yl]azetidin-1-yl}carbonyl)-2-methylpyridazin-3(2*H*)-one: ^{1}H NMR (400MHz, d_6-DMSO): 10.19 (s, 1H), 7.78 (dd, 1H), 7.59 (d, 1H), 7.32 (t, 1H), 5.95 (s, 1H), 4.59 (q, 1H), 4.13-4.27 (m, 2H), 3.77 (d, 1H), 3.62 (s, 3H), 3.02 (d, 2H), 2.71 (d, 1H), 1.78 (s, 1H), 1.68 (d, 1H), 1.53 (d, 1H), 1.32 (s, 2H), 1.17 (t, 1H); MS (EI) for $C_{20}H_{23}FIN_5O_3$: 528 (MH+).

Example 23

1-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}-3-nitroguanidine hydrochloride



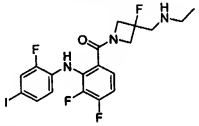
[00402] To a mixture of 2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)-6-(1-oxa-5-azaspiro[2,3]hex-5-ylcarbonyl)aniline (0.15g, 0.33 mmol), prepared using procedures similar to those described in Example 21, and nitroguanidine (0.1 g, 1.00 mmol) in tetrahydrofuran (3.00 mL) an aqueous solution of sodium hydroxide (1.0 mL, 2.0 mmol) was added and the reaction mixture was stirred at 70 °C for 16 hours. The reaction mixture was concentrated *in vacuo*. The crude product was purified by reverse phase preparative HPLC. The fractions were collected, and the solvent was concentrated. The residue was partitioned with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate, brine and dried over anhydrous sodium sulfate. Filtration and concentration resulted in an amorphous residue, which was dissolved in methanol, and 4 N HCl in dioxane (80 µL, 0.33 mmol) was added to the solution. A white precipitate formed and was collected by filtration. The solid was washed with hexane, and dried to afford 76 mg (38%) 1-{[1-({3,4-difluoro-2-[(2-

fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}-3-nitroguanidine hydrochloride. ^{1}H NMR (400 MHz, d_4-MeOH): 7.46 (2d, 1H), 7.36 (m, 1H), 7.29 (m, 1H), 7.02 (m, 1H), 6.63 (m, 1H), 4.22 (m, 1H), 4.01 (m, 2H), 3.86 (m, 1H), 3.51 (d, 2H); MS (EI) for $C_{18}H_{16}F_3IN_6O_4$: 565 (MH^+).

[00403] **EXAMPLE 23(a).** Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compounds of the invention were prepared: 1-cyano-3-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}guanidine hydrochloride. ^{1}H NMR (400 MHz, d_4-MeOH): 7.47 (2d, 1H), 7.36 (m, 1H), 7.27 (m, 1H), 7.03 (m, 1H), 6.63 (m, 1H), 4.18 (m, 1H), 3.98 (m, 2H), 3.80 (m, 1H), 3.43 (s, 2H); MS (EI) for $C_{19}H_{16}F_3IN_6O_2$: 545 (MH^+).

EXAMPLE 24

6-({3-[(ethylamino)methyl]-3-fluoroazetidin-1-yl}carbonyl)-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline



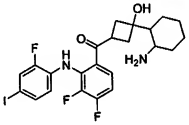
[00404] To 1,1-dimethylethyl [{1-({3,4-difuoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}ethylcarbamate (27 mg, 0.044 mmol), prepared using procedures similar to those in Example 3 and followed by Boc-protection, in chloroform (2.5 mL) added DAST (11.8 μL, 0.089 mmol) and stirred for 3.5 hr at room temperature. Quenched with water (15 mL), partitioned phases and extracted aqueous phase with chloroform (2 X 15mL). The combined chloroform extracts were dried over sodium sulfate, filtered and the filtrate concentrated *in vacuo*. The residue was purified on a silica gel column to afford 1,1-dimethylethyl [{1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-fluoroazetidin-3-yl]methyl}ethylcarbamate (19.0 mg, 70%).

[00405] To the 1,1-dimethylethyl [{1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-fluoroazetidin-3-yl]methyl}ethylcarbamate

(19.0 mg, 0.031 mmol) in acetonitrile (1.0 mL) added a solution 4.0N hydrogen chloride in dioxane (1.0 mL). After 1.5hr the solution was concentrated *in vacuo*. The residue was purified by preparative reverse phase HPLC to afford the title compound (4.30 mg, 27%). ^{1}H NMR (400MHz, $CDCl_3$): 8.25 (s, 1H), 7.33 (dd, 1H), 7.33-7.25 (m, 1H), 7.18-7.14 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.58 (m, 1H), 4.33-4.05 (br m, 4H), 3.07-2.95 (br m, 2H), 2.65 (q, 2H), 1.08 (t, 3H); MS (EI) for $C_{19}H_{18}F_4IN_3O$: 508 (MH^+).

EXAMPLE 25

3-(2-aminocyclohexyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol



[00406] A solution of 1-(trimethylsiloxy)cyclohexene (200 mg, 1.17 mmol) and benzyl 3-oxoazetidine-1-carboxylate (289 mg, 1.41 mmol), prepared using procedures similar to those described in Reference 3, in tetrahydrofuran (3.90 mL) was cooled to -78 °C for 10 minutes followed by the addition of titanium tetrachloride (0.13 mL, 1.17 mmol). The reaction mixture stirred for an additional 5 hours at -78 °C. The mixture was quenched with aqueous sodium bicarbonate and the aqueous layer was extracted with ether (2x). The organic layer was separated, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated *in vacuo*. The residue was purified on silica gel chromatography column (3:2 hexanes/ethyl acetate) to afford benzyl 3-hydroxy-3-(2-oxocyclohexyl)azetidine-1-carboxylate (328 mg, 37%) . ^{1}H NMR ($CDCl_3$): 7.28-7.34 (m, 5H), 5.08 (s, 2H), 4.02 (d, 1H), 3.89 (d, 1H), 3.87 (s, 1H), 3.55 (s, 1H), 2.71 (q, 1H), 2.29-2.43 (m, 2H), 2.11 (s, 2H), 1.95 (s, 1H), 1.66 (d, 3H); MS (EI) for $C_{17}H_{21}NO_4$: 303 (MH+).

[00407] A solution of benzyl 3-hydroxy-3-(2-oxocyclohexyl)azetidine-1-carboxylate (100 mg, 330 mmol) in methanol (1.60 mL) in the presence of ammonium acetate (191 mg, 2.48 mmol was cooled to 0 °C for 1 hour. Sodium cyanoborohydride (81.5 mg, 1.30 mmol) was added and the mixture was stirred at

room temperature for 16 hours. To the reaction mixture was added 6 N hydrogen chloride (800 μL) and extracted with ethyl acetate. The aqueous layer was basified with aqueous sodium bicarbonate (pH 9) and extracted with dichloromethane. The combined organic portion was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford benzyl-3-(2-aminocyclohexyl)-3-hydroxyazetidine-1-carboxylate (73.7 mg, 73%) . MS (EI) for $C_{17}H_{24}N_2O_3$: 305 (MH+).

[00408] To a solution of benzyl-3-(2-aminocyclohexyl)-3-hydroxyazetidine-1-carboxylate (202 mg, 0.663 mmol) in dioxane-water (1:1, 2.5 mL) was added di-*tert*-butyl dicarbonate (138 mg, 0.630 mmol) and solid sodium bicarbonate (112 mg, 1.33 mmol). The reaction mixture was stirred at room temperature for 2 hours and evaporated. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford benzyl 3-(2-*tert*-butoxycarbonylamino)cyclohexyl)-3-hydroxyazetidine-1-carboxylate (237 mg, 100%). ^{1}H NMR (CH_3OH): 7.15-7.21 (m, 5H), 5.45 (s, 0.5H), 5.20 (d, 0.5H), 4.95 (s, 2H), 4.81 (s, 1H), 3.81 (d, 2H), 1.43-1.74 (m, 5H), 1.39 (s, 1H), 1.31 (s, 11H), 1.20 (s, 1H). MS (EI) for $C_{22}H_{32}N_2O_5$: 405 (MH+).

[00409] A solution of benzyl 3-(2-tert-butoxycarbonylamino)cyclohexyl)-3-hydroxyazetidine-1-carboxylate (237 mg, 0.586 mmol) in ethyl acetate (2 mL) was hydrogenated over 10% palladium-carbon (200 mg, 0.586 mmol) at 40 psi for 16 hours. The reaction mixture was filtered and concentrated *in vacuo* to provide *tert*-butyl 2-(3-hydroxyazetidin-3-yl)cyclohexylcarbamate (181 mg, 100%). ^{1}H NMR ($CDCl_3$): 5.10 (s, 1H), 4.80 ((s, 1H), 3.78-3.86 (m, 1H), 3.61 (d, 1H), 3.57 (s, 1H), 3.36 (d, 1H), 1.77 (s, 2H). 1.40-1.53 (m, 1H), 1.36 (d, 9H), 1.25 (s, 2H). MS (EI) for $C_{14}H_{26}N_2O_3$: 271 (MH+).

[00410] To a solution of *tert*-butyl 2-(3-hydroxyazetidin-3-yl)cyclohexylcarbamate (181 mg, 0.669 mmol) and 3,4-difluoro-2-(2-fluoro-4-iodophenylamino)benzoyl fluoride (265 mg, 0.669 mmol), prepared using procedures similar to those described in Reference 1, in tetrahydrofuran (2.2 mL) was added *N,N*-diisopropylethylamine (110 μL) at room temperature. After an hour, the reaction mixture was heated to 50 °C and stirred for 45 minutes, at which time it was cooled to room temperature and evaporated. The residue was partitioned between ethyl acetate and 10% citric acid. The organic layer was washed with aqueous sodium chloride, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford *tert*-butyl-2-(1-(3,4-

difluoro-2-(2-fluoro-4-iodophenylamino)benzoyl)-3-hydroxyazetidin-3-yl)cyclohexylcarbamate. This crude material was taken into the next step without further purification.

[00411] *Tert*-butyl-2-(1-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)benzoyl)-3-hydroxyazetidin-3-yl)cyclohexylcarbamate was dissolved in a mixture of methanol (4 mL) and hydrogen chloride (4 M in dioxane) (3 mL). The solution was heated to reflux then cooled to room temperature and stirred for 16 hours. The reaction mixture was concentrated and purified by reverse phase HPLC. The purified fractions were evaporated to dryness and partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford an oil. The residue was taken up in methanol (2 mL) and was added hydrogen chloride (4M in dioxane) (700 μL) and evaporated to dryness to afford the title compound 3-(2-aminocyclohexyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol hydrochloride (44.7 mg, 12%).

^{1}H NMR (400MHz, d_6-DMSO): 8.58 (d, 1H), 7.59 (dd, 1H), 7.54 (s, 2H), 7.38 (d, 1H), 7.33 (t, 1H), 7.16-7.25 (m, 1H), 6.69 (dt, 1H), 6.41 (s, 1H), 4.26 (d, 0.5H), 4.17 (d, 0.5H), 4.04 (t, 1H), 3.90 (t, 1H), 3.79 (d, 0.5H), 3.65-3.73 (m, 0.5H), 3.45-3.51 (m, 1H), 1.88 (s, 1H), 1.65-1.88 (m, 2H), 1.47 (s, 4H), 1.16-1.37 (m, 2H); MS (EI) for $C_{22}H_{23}F_3IN_3O_2$: 546 (MH^+).

[00412] Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compounds of the invention were prepared:

EXAMPLE 25(ε).3-(2-aminocyclopentyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol; ^{1}H NMR (400MHz, d_6-DMSO): 8.56 (d, 1H), 7.82 (d, 1H), 7.59 (td, 1H), 7.45 (s, 1H), 7.38 (d, 1H), 7.30-7.35 (m, 1H), 7.18-7.24 (m, 1H), 6.68-6.72 (m, 1H0, 6.41 (s, 0.5H), 6.17 (s, 0.5H), 3.91-4.27 (m, 2.5H), 3.78-3.86 (m, 1H), 3.65-3.73 (m, 1H), 3.44-3.52 (m, 0.5H), 2.19-2.26 (m, 1H), 1.54-1.94 (m, 5H), 1.30-1.39 (m, 1H); MS (EI) for $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+).

EXAMPLE 25(a) and EXAMPLE 25(b)

(±)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(trans)-2-hydroxycyclohexyl]azetidin-3-ol

and

(±)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(cis)-2-hydroxycyclohexyl]azetidin-3-ol

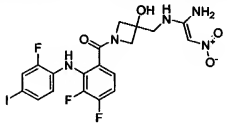
[00413] The compounds of examples 25a and 25b were synthesized starting from benzyl 3-hydroxy-3-(2-oxycyclohenyl)azetidine-1-carboxylate prepared according to the procedure given in example 25. The ketone was reduced to give benzyl 3-hydroxy-3-(2-hydroxycyclohexyl)azetidine-1-carboxylate as a mixture of racemic diastereomers which were subjected to hydrogenation to afford 3-(2-hydroxycyclohexyl)azetidin-3-ol. 3-(2-hydroxycyclohexyl)azetidin-3-ol was then carried forward in a coupling step with 3,4-difluoro-2-(2-fluoro-4-iodophenylamino)benzoyl fluoride in the usual manner. The coupled material thus obtained was purified by preparative reverse phase HPLC where fraction 1 was tentatively assigned as (±)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(trans)-2-hydroxycyclohexyl]azetidin-3-ol (Example 25a) and fraction 2 was tentatively assigned as (±)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(cis)-2-hydroxycyclohexyl]azetidin-3-ol.

EXAMPLE 25(a). First eluting fraction: ^{1}H NMR (400 MHz, d_4-MeOH): 7.44 (2d, 1H), 7.34 (t, 1H), 7.25 (m, 1H), 7.03 (m, 1H), 6.60 (m, 1H), 4.46 (d, 0.5H), 4.28 (d, 0.5H), 4.22 (d, 0.5H), 3.98 (dd, 1H), 3.89 (d, 0.5H), 3.85 (s, 0.5H), 3.77 (d, 0.5H), 3.56 (m, 1H), 1.90 (m, 1H), 1.46-1.74 (m, 4H), 0.98-1.32 (m, 4H); MS (EI) for $C_{22}H_{22}F_3IN_2O_3$: 547 (MH^+).

EXAMPLE 25(b). Second eluting fraction: ^{1}H NMR (400 MHz, d_4-MeOH): 7.44 (2d, 1H), 7.33 (d, 1H), 7.26 (m, 1H), 7.04 (m, 1H), 6.59 (dd, 1H), 4.20 (m, 1.5H), 4.19 (s, 0.5H), 4.00 (m, 1.5H), 3.86 (dd, 1H), 3.74 (d, 0.5H), 1.76 (m, 2H), 1.50-1.68 (m, 5H), 1.18-1.46 (m, 4H); MS (EI) for $C_{22}H_{22}F_3IN_2O_3$: 547 (MH^+).

Example 26

3-({[(E)-1-amino-2-nitroethenyl]amino}methyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol



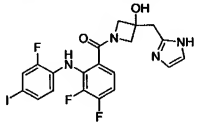
[00414] A solution of 3-(aminomethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol (0.24 g, 0.5 mmol), prepared using procedures similar to those described in Example 3, and commercially available 1,1-bis(methylthio)-2-nitroethylene (0.083 g, 0.5 mmol) in ethanol (5 mL) was stirred at 70 °C for 16 hours. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated to afford 0.10 g, (39%) 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(Z)-1-(methylthio)-2-nitroethenyl]amino}methyl)azetidin-3-ol. MS (EI) for $C_{20}H_{18}F_3IN_4O_4S$: 595 (MH^+).

[00415] To a solution of (0.05 g 0.08 mmol) 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(Z)-1-(methylthio)-2-nitroethenyl]amino}methyl)azetidin-3-ol in ethanol (2 mL) was added ammonium hydroxide (0.1 mL, 0.8 mmol) and the reaction mixture was stirred at 70 °C for 16 hours. The reaction mixture was concentrated *in vacuo*. The crude product was purified by reverse phase preparative HPLC. The fractions were collected and the solvent was concentrated. The residue was partitioned with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate, brine and dried over anhydrous sodium sulfate. Filtration and concentration resulted in an amorphous residue, which was dissolved in methanol, and 4 N HCl in dioxane (40 µL, 0.16 mmol) was added to the solution. A white precipitate formed and was collected by vacuum filtration. The solid was washed with hexane, and dried to afford 42 mg (87%) 3-({[(E)-1-amino-2-nitroethenyl]amino}methyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol hydrochloride. ^{1}H NMR (400 MHz, d_4-MeOH): 7.58 (t, 0.5H), 7.44 (t, 0.5H), 7.36 (m, 1H), 7.31 (m, 1H), 7.04 (m,

1H), 6.63 (m, 1H), 3.90-4.30 (m, 4H) 3.72 (s, 2H); MS (EI) for $C_{19}H_{17}F_3IN_5O_4$: 564 (MH^+).

EXAMPLE 27

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1*H*-imidazol-2-ylmethyl)azetidin-3-ol



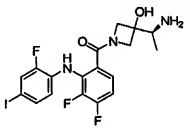
[00416] A solution of 2-methyl-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-imidazole (0.5 g, 2.3 mmol) (prepared using procedures similar to those described in Clader *et. al. J. of Med. Chem.* **1995,** *38(10),* 1600-7) in tetrahydrofuran (5 mL) was cooled to –78 °C, and *n*-butyllithium was added (2.5 M in hexanes, 0.990 mL, 2.5 mmol). After 2 hours, 1,1-dimethylethyl 3-oxoazetidine-1-carboxylate (0.60 g, 3.5 mmol), prepared using procedures similar to those described in Example 3, in 2.0 mL tetrahydrofuran was added and the solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with an excess of saturated aqueous ammonium chloride solution and partitioned between water and ethyl acetate. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 3:1 hexanes/ethyl acetate) gave 0.37 g (41%) of 3-{[1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-imidazol-2-yl]methyl}azetidin-3-ol: ^{1}H NMR (400 MHz, $CDCl_3$): 6.96-6.92 (m, 1H), 5.23 (s, 2H), 3.98 (d, 2H), 3.79 (d, 2H), 3.52-3.47 (m, 2H), 3.13 (s, 2H), 1.43 (s, 9H), 0.94-0.88 (m, 2H), 0.00 (s, 9H).

[00417] 3-{[1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-imidazol-2-yl]methyl}azetidin-3-ol (0.19 g, 0.49 mmol) was dissolved in dichloromethane (1.5 mL) and trifluoroacetic acid (1.5 mL) was added. The reaction mixture was stirred at room temperature overnight and the solvent was removed under vacuum to give 0.16 g of 3-(1*H*-imidazol-2-ylmethyl)azetidin-3-ol trifluoroacetate salt (87%). The crude residue was used without further purification for the next step.

[00418] To a solution of 3-(1*H*-imidazol-2-ylmethyl)azetidin-3-ol trifluoroacetate salt (0.16 g, 0.42 mmol) and *N,N*-diisopropylethylamine (0.370 mL, 2.13 mmol) in tetrahydrofuran (2.0 mL) 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoyl fluoride (0.17 g, 0.42 mmol), prepared using procedures similar to those described in Reference 1, was added and the reaction mixture was stirred for 3 hours at room temperature. The solution was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate and the organic layer was dried over sodium sulfate and concentrated *in vacuo*. Purification by reverse-phase HPLC followed by lyophilization of the pure fractions gave 0.032 g (13%) of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1*H*-imidazol-2-ylmethyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.45 (dd, 1H), 7.38-7.33 (m, 1H), 7.25-7.18 (m, 1H), 7.08-6.96 (m, 1H), 6.89 (s, 2H), 6.65-6.56 (m, 1H), 4.33-4.22 (m, 1H), 4.17-4.00 (m, 2H), 3.91-3.80 (m, 1H), 3.08 (s, 2H), 1.96 (s, 3H). MS (EI) for $C_{20}H_{16}F_3IN_4O_2$: 529 (MH^+).

EXAMPLE 28

3-[(1*R*)-1-aminoethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol



[00419] To a solution of diisopropylamine (6.5 mL, 46.3 mmol) in THF (200 mL) at -78 °C was added butyllithium (17 mL of a 2.5 M solution in hexanes, 42.5 mmol) over 5 min. The solution of lithium diisopropylamide was stirred for 15 min at -78 °C. A solution of (*S*)-4-benzyl-3-propionyl-2-oxazolidinone (9.0 g, 38.6 mmol) in THF (100 mL) was added to the lithium diisopropylamide by addition funnel over 26 min. The reaction temperature was kept below -70 °C during the course of the addition. After the addition, the mixture was stirred for a further 30 min at -78 °C. Then phenylmethyl 3-oxoazetidine-1-carboxylate (9.5 g, 46.3 mmol) was added by addition funnel over 25 minutes as a solution in THF (100 mL). Again, the reaction mixture was kept below -70 °C during the reagent addition. After stirring for an

additional 1 hour at -78 °C, the reaction mixture was quenched with saturated ammonium chloride solution and was then allowed to warm to rt. Water was added to dissolve any precipitated ammonium chloride, and ethyl acetate was added. The layers were partitioned, and the aqueous phase was extracted twice with ethyl acetate. The combined organic extracts were washed with 5% aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography (50% ethyl acetate: 50% hexanes) to provide phenylmethyl 3-hydroxy-3-{(1*R*)-1-methyl-2-oxo-2-[(4*S*)-2-oxo-4-(phenylmethyl)-1,3-oxazolidin-3-yl]ethyl}azetidine-1-carboxylate as a white crystalline solid (6.03 g, 13.8 mmol, 36% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 8H), 7.20 (d, 2H), 5.12 (s, 2H), 4.66 (m, 1H), 4.27-4.20 (m, 2H), 4.10 (q, 1H), 4.03-3.93 (m, 3H), 3.28 (dd, 1H), 2.77 (dd, 1H), 1.29 (d, 3H).

[00420] A solution of lithium hydroxide monohydrate (1.16 g, 27.6 mmol) in 30% hydrogen peroxide (13.2 mL, 138 mmol) was prepared and was subsequently added slowly to a solution of phenylmethyl 3-hydroxy-3-{(1*R*)-1-methyl-2-oxo-2-[(4*S*)-2-oxo-4-(phenylmethyl)-1,3-oxazolidin-3-yl]ethyl}azetidine-1-carboxylate (6.03 g, 13.8 mmol) in THF (80 mL) and water (20 mL) at 0 °C. After the mixture was stirred for 1 h at rt, the hydrogen peroxide was quenched carefully with 1 M sodium sulfite (150 mL, 150 mmol). The THF was removed *in vacuo*, and the mixture was then acidified to pH=2 with concentrated hydrochloric acid. The aqueous mixture was extracted twice with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (gradient, 5% methanol: 95% dichloromethane to 10% methanol: 90% dichloromethane) to provide (2*R*)-2-(3-hydroxy-1-{[(phenylmethyl)oxy]carbonyl}azetidin-3-yl)propanoic acid as a colorless oil (2.77 g, 9.9 mmol, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.31 (m, 5H), 5.10 (s, 2H), 3.99 (s, 2H), 3.93 (s, 2H), 2.88 (q, 1H), 1.28 (d, 3H); MS (EI) for $C_{14}H_{17}NO_5$: 280 (MH^+).

[00421] To a solution of (2*R*)-2-(3-hydroxy-1-{[(phenylmethyl)oxy]carbonyl}azetidin-3-yl)propanoic acid (2.77 g, 9.9 mmol) in toluene (100 mL) was added triethylamine (1.52 mL, 10.9 mmol) followed by diphenyl phosphoryl azide (2.24 mL, 10.4 mmol). The mixture was heated to 80 °C for 2 h and was then cooled to rt. The volatile materials were removed *in vacuo*, and

the residue was purified by column chromatography (gradient: 50% hexanes: 50% ethyl acetate up to 100% ethyl acetate). The desired product, (8*R*)-8-methyl-6-oxo-5-oxa-2,7-diazaspiro[3.4]octane-2-carboxylic acid phenylmethyl ester, was isolated as a viscous, colorless syrup (1.84 g, 6.6 mmol, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.32 (m, 5H), 5.66 (br s, 1H), 5.12 (s, 2H), 4.34 (dd, 1H), 4.30 (dd, 1H), 4.17 (dd, 1H), 4.05 (dd, 1H), 3.98 (q, 1H), 1.34 (d, 3H).

[00422] To a solution of (8*R*)-8-methyl-6-oxo-5-oxa-2,7-diazaspiro[3.4]octane-2-carboxylic acid phenylmethyl ester (1.84 g, 6.6 mmol) in methanol (66 mL) was added wet 10% palladium on carbon (50% by mass, 500 mg). The resulting suspension was stirred under 1 atm of hydrogen for 1 h. The catalyst was then removed by filtration through celite. The filtrate was concentrated *in vacuo* to provide (8*R*)-8-methyl-5-oxa-2,7-diazaspiro[3.4]octan-6-one as a white solid (0.99 g, quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (br s, 1H), 4.07 (d, 1H), 4.02 (d, 1H), 3.92 (d, 1H), 3.79 (d, 1H), 3.58 (d, 1H), 1.38 (d, 3H); MS (EI) for $C_6H_{10}N_2O_2$: 143 (MH^+).

[00423] A solution of (8*R*)-8-methyl-5-oxa-2,7-diazaspiro[3.4]octan-6-one (937 mg, 6.6 mmol), acetic acid (0.756 mL, 13.2 mmol), and benzaldehyde (1.0 mL, 9.9 mmol) in methanol (65 mL) was treated with sodium cyanoborohydride (829 mg, 13.2 mmol) at rt for 30 min. The mixture was then cooled to 0 °C, and 3 N hydrochloric acid (100 mL) was added. The methanol was then removed *in vacuo*. The resulting aqueous solution was washed with ethyl acetate. The ethyl acetate wash was back extracted with 1 N hydrochloric acid, and the aqueous acidic phases were combined and basified with potassium carbonate. The organic phase was discarded. The aqueous mixture was then extracted three times with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The desired (8*R*)-8-methyl-2-(phenylmethyl)-5-oxa-2,7-diazaspiro[3.4]octan-6-one was obtained in 93% purity as a milky colorless liquid (1.33 g, 5.73 mmol, 87% yield). MS (EI) for $C_{13}H_{16}N_2O_2$: 233 (MH^+).

[00424] To a solution of (8*R*)-8-methyl-2-(phenylmethyl)-5-oxa-2,7-diazaspiro[3.4]octan-6-one (1.33 g, 5.7 mmol) in dioxane (40 mL) and water (20 mL) was added barium hydroxide octahydrate (9.0 g, 28.5 mmol), and the mixture was heated to reflux for 2 h. After cooling to rt, the mixture was acidified with 3 N hydrochloric acid (10 mL) and dichloromethane (50 mL) was added. The biphasic

mixture was treated with potassium carbonate (1.6 g, 11.4 mmol) and di-*tert*-butyl dicarbonate (2.11 g, 9.7 mmol). After stirring vigorously at rt for 17 h, solids were removed by filtration, and the layers were partitioned. The aqueous phase was extracted with dichloromethane, and the organic extracts were combined and dried over magnesium sulfate, filtered, and concentrated. The residue was taken up in methanol (60 mL) and was treated with potassium carbonate (3.0 g, 22 mmol) added in two portions over 4 h at reflux. After cooling, the methanol was removed *in vacuo*, and the residual solids were loaded directly on to a silica column. After purification (5% methanol: 95% dichloromethane), 1,1-dimethylethyl {(1*R*)-1-[3-hydroxy-1-(phenylmethyl)azetidin-3-yl]ethyl}carbamate was obtained as a colorless syrup (1.07 g, 3.5 mmol, 62% yield). MS (EI) for $C_{17}H_{26}N_2O_3$: 307 (MH^+).

[00425] To a solution of 1,1-dimethylethyl {(1*R*)-1-[3-hydroxy-1-(phenylmethyl)azetidin-3-yl]ethyl}carbamate (1.07 g, 3.5 mmol) in methanol was added wet 10% palladium on carbon (50% by mass, 250 mg). The resulting suspension was subjected to 1 atmosphere of hydrogen for 7 h, and an additional 250 mg of catalyst was added over the course of the reaction. The catalyst was then removed by filtration through celite. The filtrate was then concentrated *in vacuo* to provide 1,1-dimethylethyl [(1*R*)-1-(3-hydroxyazetidin-3-yl)ethyl]carbamate as a colorless syrup (800 mg, quantitative yield). MS (EI) for $C_{10}H_{20}N_2O_3$: 161 (M - *tert*-butyl + H).

[00426] To a solution of 1,1-dimethylethyl [(1*R*)-1-(3-hydroxyazetidin-3-yl)ethyl]carbamate (200 mg, 0.92 mmol) in dichloromethane (5 mL) was added diisopropylethylamine (228 μL, 1.38 mmol) and 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoyl fluoride (prepared according to the procedures described in Reference 1) (363 mg, 0.92 mmol). The mixture was stirred at rt for 16 h, after which the volatile materials were removed *in vacuo*. The residue was purified by column chromatography (50% hexanes : 50% ethyl acetate) to provide 1,1-dimethylethyl {(1*R*)-1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}carbamate as a colorless film (333 mg, 0.56 mmol, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (br s, 1H), 7.40 (dd, 1H), 7.32 (d, 1H), 7.12 (m, 1H), 6.81 (m, 1H), 6.61 (m, 1H), 4.74 (br d, 1H), 4.22 (d, 1H), 4.15-4.07 (m, 2H), 3.96 (br s, 1H), 3.77 (m, 1H), 1.43 (s, 9H), 1.18 (d, 3H); MS (EI) for $C_{23}H_{25}F_3IN_3O_4$: 536 (M - *tert*-butyl + H).

[00427] A solution of 1,1-dimethylethyl {(1*R*)-1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}carbamate (333 mg, 0.56 mmol) in methanol (10 mL) was treated with hydrochloric acid (4 N in dioxane, 1.4 mL, 5.6 mmol) at 60 °C for 30 min. After cooling, the volatile materials were removed *in vacuo* to provide 3-[(1*R*)-1-aminoethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol hydrochloride as a white solid (285 mg, 0.54 mmol, 97% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1H), 7.83 (br s, 3H), 7.59 (dd, 1H), 7.39 (d, 1H), 7.34 (m, 1H), 7.21 (q, 1H), 6.69 (m, 1H), 6.65 (s, 1H), 4.25 (dd, 1H), 4.10 (dd, 1H), 3.98 (dd, 1H), 3.80 (m, 1H), 3.48 (m, 1H), 1.11 (dd, 3H); MS (EI) for $C_{18}H_{17}F_3IN_3O_2$: 492 (MH^+)

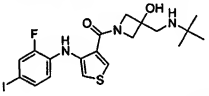
[00428] To establish the enantiomeric excess (ee) of this material, 3-[(1*R*)-1-aminoethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol hydrochloride (21 mg, 0.040 mmol) was dissolved in dichloromethane (400 μL) and was treated with diisopropylethylamine (20 μL, 0.12 mmol) and (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride at rt for 15 min. An aliquot was removed and was analyzed by chiral HPLC. The diastereomeric excess of (2*S*)-N-{(1*R*)-1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanamide was found to be 91%, and by extrapolation the ee of 3-[(1*R*)-1-aminoethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol was also assigned to be 91%.

[00429] **Example 28a.** Using the sequence described above, beginning with (*R*)-4-benzyl-3-propionyl-2-oxazolidinone, 3-[(1*S*)-1-aminoethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol was prepared using similar procedures except that the phenylmethyl 3-hydroxy-3-{(1*S*)-1-methyl-2-oxo-2-[(4*R*)-2-oxo-4-(phenylmethyl)-1,3-oxazolidin-3-yl]ethyl}azetidine-1-carboxylate required additional recrystallizations from isopropanol. Using the same method described above in Example 28, 3-[(1*S*)-1-aminoethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol was determined to have 98.4% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1H), 7.84 (br s, 3H), 7.59 (dd, 1H), 7.39 (d, 1H), 7.34 (m, 1H), 7.21 (q, 1H), 6.69 (m, 1H), 6.65 (s, 1H), 4.25 (dd, 1H), 4.10 (dd, 1H), 3.98 (dd, 1H), 3.80 (m, 1H), 3.48 (m, 1H), 1.11 (dd, 3H); MS (EI) for $C_{18}H_{17}F_3IN_3O_2$: 492 (MH^+).

[00430] **Example 28b.** To 3-[(1*S*)-1-aminoethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol (87.4 mg, 0.18 mmol), prepared using procedures similar to those described in Example 28, was added formaldehyde (37% aqueous, 14 mg, 0.18 mmol) in methanol (2 mL) and sodium borohydride (7 mg, 0.18 mmol). The mixture was stirred for 3 h at rt, after which sodium borohydride (16 mg, 0.42 mmol) was added. Upon stirring an additional 1.25 h, more formaldehyde (37% aqueous, 1 drop) was added, and the mixture was stirred 3 days at rt. A further small spatula (~50 mg) of sodium borohydride was then added, and the mixture was stirred at rt for 30 min. After quenching with 1 N HCl, the reaction mixture was purified directly by preparative HPLC. The clean material was converted to its hydrochloride salt to provide 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(1*S*)-1-(methylamino)ethyl]azetidin-3-ol as a yellow solid (21.7 mg, 0.040 mmol, 22% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (dd, 1H), 7.36 (d, 1H), 7.31 (m, 1H), 7.06 (q, 1H), 6.62 (dt, 1H), 4.36 (dd, 1H), 4.21-3.91 (m, 3H), 3.44 (q, 1H), 2.66 (s, 3H), 1.29 (br m, 3H); MS (EI) for $C_{19}H_{19}F_3IN_3O_2$: 506 (MH^+).

EXAMPLE 29

3-{[(1,1-Dimethylethyl)amino]methyl}-1-({4-[(2-fluoro-4-iodophenyl)amino]-3-thienyl}carbonyl)azetidin-3-ol



[00431] To a mixture of methyl 4-oxotetrahydrothiophene-3-carboxylate (1.75 g, 11 mmol) (commercially available or prepared using procedures similar to those described in Rossy *et. al. J. Org. Chem.* **1980,** *45(4),* 617-2) in 15 mL of ethanol was added 2-fluoro-4-iodoaniline (2.6 g, 11 mmol) followed by addition of several drops of acetic acid . The mixture was refluxed for 3 hrs. The mixture was cooled to room temperature and the product precipitated. This product was filtered off, washed with ethyl acetate, ether, dried *in vacuo* to afford the methyl 4-[(2-fluoro-4-iodophenyl)amino]-2,5-dihydrothiophene-3-carboxylate (1.7 g, 42%). ^{1}HNMR(d_6-DMSO):9.80 (s,1H), 7.71 (d, 1H), 7.49 (dd, 1H), 7.24 (t, 1H), 4.10 (t, 2H), 3.79 (t, 2H), 3.69 (s, 3H); MS(EI) for $C_{12}H_{11}FINO_2S$: 380 (MH^+).

[00432] To a mixture of methyl 4-[(2-fluoro-4-iodophenyl)amino]-2,5-dihydrothiophene-3-carboxylate (1.2 g, 3.16 mmol) in 10 ml of anhydrous toluene was added 2,3,5,6-tetrachlorocyclohexa-2,5-diene-1,4-dione (0.78 g, 3.16 mmol). The mixture was refluxed for 2 h. The mixture was cooled to 50 °C and concentrated *in vacuo* to dryness and cooled to room temperature. To the residue was added ethanol and the mixture was refluxed for several minutes, cooled to room temperature and light blue crystalline product was filtered off and dried *in vacuo* to afford methyl 4-[(2-fluoro-4-iodophenyl)amino]thiophene-3-carboxylate (0.74 g, 62%). ^{1}HNMR(d_6-DMSO): 8.78 (s, 1H), 8.42(d, 1H), 7.64 (d, 1H), 7.46 (d, 1H), 7.37(t, 1H), 7.14 (s, 1H), 3.85(s, 3H); MS(EI) for $C_{12}H_9FINO_2S$: 378 (MH^+).

[00433] A mixture of methyl 4-[(2-fluoro-4-iodophenyl)amino]thiophene-3-carboxylate (0.74g, 1.96 mmol) in the solution of potassium hydroxide (0.3g) in ethanol / water (4ml/4ml) was heated up to 60 °C and stirred at this temperature for 30 min. The mixture was cooled to room temperature, diluted with 4 ml of water and extracted with ether. The water layer was acidified with 1 N HCl to pH 2, the product precipitated and was filtered off, washed several times with water and dried *in vacuo* to afford 4-[(2-fluoro-4-iodophenyl)amino]thiophene-3-carboxylic acid (0.59 g, 83%). ^{1}H NMR (d_6-DMSO): 13.20(s, 1H), 9.13 (s, 1H), 8.35 (d, 1H), 7.62 (dd, 1H), 7.48-7.38 (m, 2H), 7.11 (s, 1H); MS(EI) for $C_{11}H_7FINO_2S$: 362 (MH^+).

[00434] 4-[(2-fluoro-4-iodophenyl)amino]thiophene-3-carboxylic acid (200 mg, 0.551 mmol), 4-(dimethylamino)pyridine (202 mg, 1.65 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (127 mg, 0.662 mmol) were dissolved in DMF (3 mL). The mixture was stirred at ambient for 5 minutes and then 3-(hydroxymethyl)azetidin-3-ol hydrochloride (72 mg, 0.516 mmol) was added and the mixture was stirred for 15 h. The mixture was partitioned between ethyl acetate and 20% citric acid. The aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with 5% lithium chloride, saturated sodium bicarbonate and brine, then was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was crystallized from dichloromethane to afford 1-({4-[(2-fluoro-4-iodophenyl)amino]-3-thienyl}carbonyl)-3-(hydroxymethyl)azetidin-3-ol (247 mg, 0.551 mmol, quantitative yield) as off-white crystals: MS (EI) for $C_{15}H_{14}FIN_2O_3S$: 449 (MH^+).

[00435] 1-({4-[(2-Fluoro-4-iodophenyl)amino]-3-thienyl}carbonyl)-3-(hydroxymethyl)azetidin-3-ol (247 mg, 0.551 mmol), was suspended in

dichloromethane (10 mL) and treated with 4-(dimethylamino)pyridine (80 mg, 0.661 mmol), and 2,4,6-triisopropylbenzenesulfonyl chloride (183 mg, 0.604 mmol) at ambient for 15 h. The mixture was adsorbed on to silica and purified by column chromatography (silica gel, 30% ethyl acetate in hexanes) to give [1-({4-[(2-fluoro-4-iodophenyl)amino]-3-thienyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl 2,4,6-tris(1-methylethyl)benzenesulfonate (101 mg, 0.141 mmol, 26% yield): MS (EI) for $C_{30}H_{36}FIN_2O_5S_2$: 715 (MH^+).

[00436] [1-({4-[(2-Fluoro-4-iodophenyl)amino]-3-thienyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl 2,4,6-tris(1-methylethyl)benzenesulfonate (101 mg, 0.141 mmol) was dissolved in tetrahydrofuran (2 mL) and was treated with sodium hydride (60 wt% dispersion in oil; 17 mg, 0.425 mmol) at ambient for 20 minutes. Tetrahydrofuran (2 mL) and *tert*-butylamine (0.1 mL) were added and the mixture was stirred at ambient for 16 h. The mixture was concentrated *in vacuo* and partitioned between ethyl acetate and water. The organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by reverse phase HPLC and the clean fractions were combined, neutralized with saturated sodium bicarbonate solution and the organic solvent was removed *in vacuo*. The remaining aqueous residue was extracted twice with ethyl acetate. The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford 3-{[(1,1-dimethylethyl)amino]methyl}-1-({4-[(2-fluoro-4-iodophenyl)amino]-3-thienyl}carbonyl)azetidin-3-ol (8 mg, 0.016 mmol, 11% yield): ^{1}H NMR (400 MHz, d_6-DMSO): 9.64 (br, 1H), 8.08 (d, 1H), 7.59 (dd, 1H), 7.44 (dd, 1H), 7.36 (t, 1H), 7.12 (d, 1H), 4.39 (d, 1H), 4.22 (d, 1H), 4.03 (d, 1H), 3.80 (d, 1H), 2.68 (br, 2H) 1.04 (s, 9H); MS (EI) for $C_{19}H_{23}FIN_3O_2S$: 504 (MH^+).

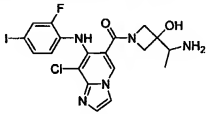
[00437] Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compounds of the invention were prepared:

EXAMPLE 29(a). 3-[(dimethylamino)methyl]-1-({4-[(2-fluoro-4-iodophenyl)amino]-3-thienyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.91 (d, 1H), 7.46- 7.41 (m, 2H), 7.33 (t, 1H), 7.00 (d, 1H), 4.66 (s, 1H), 4.49 (s, 1H), 4.30 (s, 1H), 4.15 (s, 1H), 3.54 (s, 1H), 3.17- 3.13 (m, 3H), 2.90 (s, 2H), 1.87- 1.83 (m, 3H); MS(EI) for $C_{17}H_{19}FIN_3O_2S$: 476 (MH^+).

EXAMPLE 29(b). 1-({4-[(2-fluoro-4-iodophenyl)amino]-3-thienyl}carbonyl)azetidin-3-amine: ^{1}H NMR (400 MHz, CD_3OD): 7.90 (d, 1H), 7.46-7.41 (m, 2H), 7.31 (t, 1H), 6.99 (d, 1H), 4.47 (br.s, 2H), 4.22-4.16 (m, 2H); MS(EI) for $C_{14}H_{13}FIN_3OS$: 418 (MH^+).

EXAMPLE 30

3-(1-aminoethyl)-1-({8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-a]pyridin-6-yl}carbonyl)azetidin-3-ol



[00438] To a suspension of sodium hydride (72 mg, 1.75 mmol, 60% wt) in tetrahydrofuran (1 mL) cooled to 0 °C was added nitroethane (125 μL, 1.75 mmol). The suspension was allowed to warm to room temperature and was stirred for 15 minutes, then cooled back to 0 °C. To the suspension was added dropwise a solution of 1,1-dimethylethyl 3-oxoazetidine-1-carboxylate (300 mg, 1.75 mmol, in 2 mL of tetrahydrofuran), prepared using procedures similar to those described in Reference 3. The suspension was stirred at room temperature for 1 hour. The reaction mixture was quenched by adding 20% aqueous citric acid, and then was partitioned with ethyl acetate. The aqueous portion was extracted twice using ethyl acetate and the combined organic portion was washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a colorless oil that was purified by column chromatography. Eluting with 30% ethyl acetate in hexanes, the isolated product was concentrated *in vacuo* to afford 250 mg, 1.02 mmol (58%) of 1,1-dimethylethyl 3-hydroxy-3-(1-nitroethyl)azetidine-1-carboxylate as a colorless oil. ^{1}H NMR (400 MHz, DMSO): 6.46 (s, 1H), 5.01 (q, 1H), 4.24-3.97 (m, 2H), 3.77-3.60 (m, 2H), 1.41 (d, 3H), 1.39 (s, 9H).

[00439] 1,1-Dimethylethyl 3-hydroxy-3-(1-nitroethyl)azetidine-1-carboxylate was dissolved in methanol (5 mL) and treated with 4 N HCl in dioxane. The solution was briefly heated to reflux and then was concentrated *in vacuo* to afford 178 mg, 0.98 mmol (96%) of 3-(1-nitroethyl)azetidin-3-ol hydrochloride as a white solid. ^{1}H NMR

(400 MHz, DMSO): 9.30 (br s, 1H), 8.96 (br s, 1H), 5.12 (q, 1H), 4.44-4.38 (m, 1H), 4.22-4.17 (m, 1H), 3.94-3.87 (m, 1H), 3.85-3.77 (m, 1H), 1.44 (d, 3H).

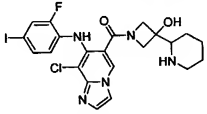
[00440] A solution of 8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-*a*]pyridine-6-carboxylic acid (150 mg, 0.35 mmol) (prepared using procedures similar to those described in US 2006030610 and US 2005054701), *N,N*-diisopropylethylamine (300 μL, 1.74 mmol), PyBOP (180 mg, 0.35 mmol) and 3-(1-nitroethyl)azetidin-3-ol hydrochloride (76 mg, 0.42 mmol) in dimethylformamide (3 mL) was stirred at room temperature for 15 hours. The reaction mixture was then partitioned between 5% aqueous lithium chloride, and ethyl acetate. The aqueous portion was extracted twice using ethyl acetate. The combined organic portion was washed with 20% aqueous citric acid, brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a brown residue which was purified by column chromatography. Eluting with 5% methanol in dichloromethane, the isolated product was concentrated *in vacuo* to afford 195 mg, 0.35 mmol (100%) of 1-({8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-*a*]pyridin-6-yl}carbonyl)-3-(1-nitroethyl)azetidin-3-ol as a yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$): 8.28 (s, 1H), 7.68 (s, 1H), 7.59 (s, 1H), 7.43 (d, 1H), 7.31 (d, 1H), 7.23 (br s, 1H), 6.55-6.51 (m, 1H), 6.02 (br s, 1H), 4.79 (q, 1H), 4.45-3.96 (4H), 1.56 (d, 3H). MS (EI) for $C_{20}H_{19}ClFIN_6O_4$: 560 (MH^+).

[00441] To a solution of 1-({8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-*a*]pyridin-6-yl}carbonyl)-3-(1-nitroethyl)azetidin-3-ol (195 mg 0.35 mmol) in tetrahydrofuran/water (5 mL, 4:1) was added iron powder (193 mg, 3.5 mmol) and ammonium formate (438 mg, 7.0 mmol). The mixture was stirred at 80°C for 1 hour, then cooled to room temperature and filtered through a pad of celite. The celite was washed three times with boiling ethanol (20 mL). The filtrate was concentrated *in vacuo* and the residue was diluted with ethyl acetate. The precipitate which formed was filtered through a pad a celite and the filtrate was partitioned with water. The aqueous portion was extracted twice with ethyl acetate. The combined organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a yellow residue which was purified by preparative reverse phase HPLC. The isolated product was concentrated *in vacuo* to afford 35 mg, 0.05 mmol (15%) of 3-(1-aminoethyl)-1-({8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-a]pyridin-6-yl}carbonyl)azetidin-3-ol acetate salt as a

white solid. ^{1}H NMR (400 MHz, DMSO): 8.79 (s, 1H), 8.00 (s, 1H), 7.61 (s, 1H), 7.54 (d, 1H), 7.32 (d, 1H), 6.54-6.48 (m, 1H), 4.24-4.13 (m, 1H), 3.98-3.84 (m, 2H), 3.61-3.56 (m, 1H), 2.83 (q, 1H), 0.92-0.88 (m, 3H); MS (EI) for $C_{19}H_{18}ClFIN_5O_2$: 530 (MH^+).

EXAMPLE 31

1-({8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-a]pyridin-6-yl}carbonyl)-3-piperidin-2-ylazetidin-3-ol



[00442] To a solution of 1,1-dimethylethyl 2-(3-hydroxy-1-{[(phenylmethyl)oxy]carbonyl}azetidin-3-yl)piperidine-1-carboxylate (595 mg, 1.52 mmol), prepared using procedures similar to those described in Reference 5, in methanol (5 mL) was added catalytic palladium on carbon (5% wt). The heterogeneous mixture was stirred under a hydrogen gas atmosphere for 15 hours at ambient pressure and then was filtered. The filtrate was concentrated *in vacuo* to afford 385 mg, 1.50 mmol (98%) of 1,1-dimethylethyl 2-(3-hydroxyazetidin-3-yl)piperidine-1-carboxylate as a colorless film without further purification.

[00443] A solution of 8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-*a*]pyridine-6-carboxylic acid (78 mg, 0.18 mmol) (prepared using procedures similar to those described in US 2006030610 and US 2005054701), 1,1-dimethylethyl 2-(3-hydroxyazetidin-3-yl)piperidine-1-carboxylate (46.7 mg, 0.18 mmol), 4-(dimethylamino)pyridine (66 mg, 0.55 mmol), and finally 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (42 mg, 0.21 mmol) in dimethylformamide (2 mL) was stirred at room temperature for 15 hours. The reaction mixture was partition between 5% aqueous lithium chloride and ethyl acetate and the aqueous portion was extracted twice using ethyl acetate. The combined organic portion was washed with 1 N HCl, brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a brown residue which was purified by column chromatography. Eluting with ethyl acetate, the isolated product was concentrated *in vacuo* to afford 101 mg, 0.15 mmol (83%) of 1,1-dimethylethyl 2-[1-({8-chloro-7-[(2-

fluoro-4-iodophenyl)amino]imidazo[1,2-a]pyridin-6-yl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate as a white solid. The solid was immediately dissolved in methanol (5 mL) and 4 N HCl in dioxane was added. The solution was briefly heated to reflux and then was concentrated *in vacuo*. The resultant residue was purified by preparative reverse phase HPLC. Isolated product was concentrated *in vacuo* to afford 36 mg, 0.06 mmol (40%) of 1-({8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-a]pyridin-6-yl}carbonyl)-3-piperidin-2-ylazetidin-3-ol acetate as a white solid. ^{1}H NMR (400 MHz, DMSO): 8.78 (s, 1H), 8.19 (s, 0.5H), 8.15 (s, 0.5H), 8.00 (s, 1H), 7.62 (s, 1H), 7.55 (d, 1H), 7.31 (d, 1H), 6.54-6.49 (m, 1H), 4.24-4.12 (m, 1H), 3.97-3.86 (m, 2H), 3.63-3.56 (m, 1H), 2.98-2.90 (m, 1H), 2.50-2.40 (m, 1H), 1.72-1.61 (m, 1H), 1.56-1.43 (m, 2H), 1.32-1.14 (m, 2H), 1.07-0.94 (m, 1H); MS (EI) for $C_{22}H_{22}ClFIN_5O_2$: 570 (MH^+).

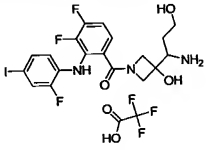
[00444] Using the same or analogous synthetic techniques and/or substituting with alternative reagents, the following compounds of the invention were prepared:

EXAMPLE 31(a). 1-({4-fluoro-5-[(2-fluoro-4-iodophenyl)amino]-1-methyl-1*H*-benzimidazol-6-yl}carbonyl)-3-piperidin-2-ylazetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.35 (s, 1H), 7.84-7.77 (m, 1H), 7.54-7.49 (m, 2H), 7.25 (d, 1H), 6.31-6.25 (m, 1H), 4.04-3.92 (m, 2H), 3.90 (s, 3H), 3.86-3.78 (m, 1H), 3.70-3.62 (m, 1H), 2.94-2.85 (m, 1H), 2.45-2.32 (m, 2H), 1.66-1.36 (m, 3H), 1.26-1.08 (m, 2H), 1.01-0.80 (m, 1H); MS (EI) for $C_{23}H_{24}F_2IN_5O_2$: 568 (MH^+).

EXAMPLE 31(a). 1-({7-[(4-bromo-2-chlorophenyl)amino]-8-chloroimidazo[1,2-a]pyridin-6-yl}carbonyl)-3-piperidin-2-ylazetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.87 (s, 1H), 8.29 (s, 0.5H), 8.21 (s, 0.5H), 8.04 (s, 1H), 7.67-7.63 (m, 2H), 7.32 (d, 1H), 6.59 (d, 1H), 4.35-4.22 (m, 1H), 4.08-3.98 (m, 2H), 3.72-3.67 (m, 1H), 2.96-2.88 (m, 1H), 2.50-2.44 (m, 2H), 1.66-1.42 (m, 3H), 1.26-1.17 (m, 2H), 1.04-0.94 (m, 1H); MS (EI) for $C_{22}H_{22}BrCl_2N_5O_2$: 540 (MH^+).

EXAMPLE 32

3-(1-Amino-3-hydroxypropyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol trifluoroacetate salt



[00445] Potassium *tert*-butoxide (1.393 g, 12.4 mmol) and [2-(1,3-dioxolan-2-yl)ethyl]-triphenylphosphonium bromide (5.51 g, 12.4 mmol) were stirred in ether (30 mL) at amibient for 1 h. Phenylmethyl 3-oxoazetidine-1-carboxylate (1.025 g, 5.0 mmol), prepared using procedures similar to those described in Reference 3, was added and the mixture was stirred at 35 °C for 6 h and then at ambient for 4 days. Mixture was filtered through celite and the solid was washed with ether. The filtrate was washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 20% ether in hexanes) gave phenylmethyl 3-[2-(1,3-dioxolan-2-yl)ethylidene]azetidine-1-carboxylate (220 mg, 0.761 mmol, 15% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 7.39-7.28 (m, 5H), 5.43-5.35 (m, 1H), 5.11 (s, 2H), 4.89 (t, 1H), 4.56 (br d, 4H), 4.00-3.92 (m, 2H), 3.91-3.83 (m, 2H), 2.27 (br t, 2H).

[00446] Phenylmethyl 3-[2-(1,3-dioxolan-2-yl)ethylidene]azetidine-1-carboxylate (220 mg, 0.761 mmol), and 4-methylmorpholine N-oxide (287 mg, 2.45 mmol) were dissolved in acetone / water (4:1; 10 mL) and osmium tetroxide (4 wt.% in water; 0.05 mL) was added. The solution was stirred at ambient for 20 h, then was quenched with saturated sodium bisulfite (2 mL) and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and brine. The aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, ethyl acetate) gave phenylmethyl 3-[2-(1,3-dioxolan-2-yl)-1-hydroxyethyl]-3-hydroxyazetidine-1-carboxylate (244 mg, 0.755 mmol, 99% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 7.38-7.28 (m, 5H), 5.11-5.07 (m, 3H), 4.14-4.01 (m, 4H), 3.96-3.86 (m, 5H), 3.47 (d, 1H), 2.97-2.94 (m, 1H), 1.98-1.84 (m, 2H).

[00447] Phenylmethyl 3-[2-(1,3-dioxolan-2-yl)-1-hydroxyethyl]-3-hydroxyazetidine-1-carboxylate (235 mg, 0.728 mmol) was dissolved in methanol (5 mL) and treated with 5 wt% palladium on carbon (50 mg) under hydrogen at ambient for 1.5 h. The mixture was filtered and the filtrate was concentrated *in vacuo* to afford 3-[2-(1,3-dioxolan-2-yl)-1-hydroxyethyl]azetidin-3-ol (0.729 mmol): MS (EI) for $C_8H_{15}NO_4$: 190 (MH^+).

[00448] 3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid (287 mg, 0.730 mmol), prepared using procedures similar to those described in US 7,019,033, 4-(dimethylamino)pyridine (178 mg, 1.46 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (168 mg, 0.88 mmol) were dissolved in DMF (3 mL). The mixture was stirred at ambient for 10 minutes and then 3-[2-(1,3-dioxolan-2-yl)-1-hydroxyethyl]azetidin-3-ol (0.729 mmol) in DMF (2 mL) was added and the mixture was stirred for 15 h. The mixture was partitioned between ethyl acetate and 5% lithium chloride. The organic portion was washed with 20% citric acid, saturated sodium bicarbonate and brine, then was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, gradient 90% ethyl acetate in hexanes to 100% ethyl acetate) gave 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[2-(1,3-dioxolan-2-yl)-1-hydroxyethyl]azetidin-3-ol (148 mg, 0.262 mmol, 36% yield): MS (EI) for $C_{21}H_{20}F_3IN_2O_5$: 565 (MH^+).

[00449] 1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[2-(1,3-dioxolan-2-yl)-1-hydroxyethyl]azetidin-3-ol (148 mg, 0.262 mmol), was dissolved in dichloromethane (10 mL) and treated with 4-(dimethylamino)pyridine (38 mg, 0.31 mmol), triethylamine (0.036 mL, 0.262 mmol) and 2,4,6-triisopropylbenzenesulfonyl chloride (303 mg, 1.0 mmol) at 35 °C for 15 h. 2,4,6-Triisopropylbenzenesulfonyl chloride (100 mg, 0.33 mmol) was added and the mixture was stirred at 35 °C for 3.5 h. The mixture was adsorbed on to silica and purified by column chromatography (silica gel, 40-50% ethyl acetate in hexanes and then 100% ethyl acetate) to give 1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]-2-(1,3-dioxolan-2-yl)ethyl 2,4,6-tris(1-methylethyl)benzenesulfonate (30 mg, 0.0361 mmol, 14% yield): MS (EI) for $C_{36}H_{42}F_3IN_2O_7S$: 831 (MH^+).

[00450] 1-[1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]-2-(1,3-dioxolan-2-yl)ethyl 2,4,6-tris(1-

methylethyl)benzenesulfonate (50 mg, 0.060 mmol) was dissolved in tetrahydrofuran (1 mL) and was cooled to 0 °C. Sodium hydride (60 wt% dispersion in oil; 7 mg, 0.18 mmol) was added and the mixture was stirred at 0 °C for 45 minutes. The mixture was quenched with saturated sodium bicarbonate solution and partitioned with ethyl acetate. The aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 50% ethyl acetate in hexanes) gave 6-{[2-(1,3-dioxolan-2-ylmethyl)-1-oxa-5-azaspiro[2.3]hex-5-yl]carbonyl}-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline (31 mg, 0.057 mmol, 94% yield): MS (EI) for $C_{21}H_{18}F_3IN_2O_4$: 547 (MH^+).

[00451] 6-{[2-(1,3-Dioxolan-2-ylmethyl)-1-oxa-5-azaspiro[2.3]hex-5-yl]carbonyl}-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline (31 mg, 0.057 mmol) was dissolved in dimethylformamide (0.5 mL) and sodium azide (20 mg, 0.308 mmol) was added. The mixture was stirred at ambient for 22 h. The mixture was partitioned between ethyl acetate and 5% lithium chloride. The aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with water, brine, then was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 50% ethyl acetate in hexanes) gave 3-[1-azido-2-(1,3-dioxolan-2-yl)ethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol (25 mg, 0.042 mmol, 74% yield): MS (EI) for $C_{21}H_{19}F_3IN_5O_4$: 590 (MH^+).

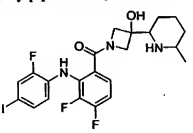
[00452] 3-[1-Azido-2-(1,3-dioxolan-2-yl)ethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol (24 mg, 0.041 mmol) was dissolved in tetrahydrofuran (0.5 mL) and treated with 5% aqueous hydrochloric acid (0.5 mL) at ambient for 15 h. The misture was neutralised with saturated sodium bicarbonate solution and was extracted twice with ethyl acetate. The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford 3-azido-3-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]propanal (21 mg, 0.0385 mmol) which was suspended in ethanol (2 mL) and treated with sodium borohydride (5 mg, 0.132 mmol) at ambient for 2 h. The mixture was quenched with acetic acid (4 drops) and concentrated *in vacuo*. The residue was partitioned between saturated sodium bicarbonate solution and ethyl acetate. The aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over

anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 70-80% ethyl acetate in hexanes) gave 3-(1-azido-3-hydroxypropyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol (14 mg, 0.0255 mmol, 62% yield from 3-[1-azido-2-(1,3-dioxolan-2-yl)ethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol): ^{1}H NMR (400 MHz, $CDCl_3$): 8.33 (br s, 1H), 7.40 (dd, 1H), 7.32 (br d, 1H), 7.13 (br t, 1H), 6.83 (br q, 1H), 6.61 (ddd, 1H), 4.32-3.94 (m, 4H), 3.92-3.84 (m, 1H), 3.82-3.71 (m, 2H), 2.56 (br, 1H), 1.94 (br, 2H), 1.26 (br, 1H); MS (EI) for $C_{19}H_{17}F_3IN_5O_3$: 548 (MH^+).

[00453] 3-(1-Azido-3-hydroxypropyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol (14 mg, 0.0255 mmol) was dissolved in tetrahydrofuran and water (1:1, 0.5 mL) and polymer supported triphenylphosphine (~3 mmol/g; 20 mg, 0.06 mmol) was added. The mixture was stirred at 55 °C for 1 h. Triphenylphosphine (10 mg, 0.038 mmol) was added and the mixture was stirred at 55 °C for 1.5 h. The mixture was filtered and the filtrate was purified by reverse phase HPLC to afford 3-(1-amino-3-hydroxypropyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol trifluoroacetate salt (1.7 mg, 0.003 mmol, 10% yield): ^{1}H NMR (400 MHz, CD_3OD): 7.47 (dd, 1H), 7.36 (br d, 1H), 7.33-7.28 (m, 1H), 7.05 (br q, 1H), 6.62 (ddd, 1H), 4.38-4.26 (m, 1H), 4.18-4.00 (m, 2H), 3.98-3.88 (m, 1H), 3.78-3.67 (m, 2H), 3.61-3.56 (m, 1H), 1.87-1.70 (m, 2H); MS (EI) for $C_{19}H_{19}F_3IN_3O_3$: 522 (MH^+).

EXAMPLE 33

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(6-methylpiperidin-2-yl)azetidin-3-ol



[00454] To a solution of *N,N*-diisopropylamine (1.6 mL, 11.2 mmol) cooled to -78 °C in THF (15 mL) was added a 2.5 M solution of n-BuLi in hexane (4.5 mL, 11.2 mmol) dropwise over 5 minutes and the mixture was stirred at this temperature for an

addition 15 minutes. 6-methyl-1-(phenylmethyl)piperidine-2-carbonitrile (2.4 g, 11.2 mmol) (prepared using procedures similar to those in Bonin *et. al. Tet. Lett.* **1982,** *23(33),* 3369-72) in THF (10 mL) was then added dropwise over 20 minutes and the reaction mixture was stirred for a further 30 minutes. Next a solution of 1,1-dimethylethyl 3-oxoazetidine-1-carboxylate (1.3 g, 7.5 mmoL), prepared using procedures similar to those in Example 3, in THF (10 mL) was added dropwise over 30 minutes. The reaction mixture was gradually warmed to room temperature and allowed to stir overnight. The reaction mixture was quenched with 10% citric acid and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water, brine, dried over anhydrous sodium sulfate then filtered and concentrated *in vacuo* to give crude product as yellow oil. Further purification by flash chromatography (30% ethyl acetate in hexanes) afforded 1,1-dimethylethyl 3-[2-cyano-6-methyl-1-(phenylmethyl)piperidin-2-yl]-3-hydroxyazetidine-1-carboxylate as a pale yellow oil (0.2 g, 7% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 7.17-7.40 (m, 5H), 4.42 (d, 1H), 4.04-4.18 (m, 1H), 3.83-4.00 (m, 1H), 3.70-3.75 (m, 2H), 1.70-1.87 (m, 4H), 1.45 (s, 3H), 1.41 (s, 9H), 1.22-1.26 (m,1H), 1.13-1.18 (m, 2H); MS (EI) for $C_{22}H_{31}N_3O_3$: 386 (MH^+).

[00455] To a stirred solution of 1,1-dimethylethyl 3-[2-cyano-6-methyl-1-(phenylmethyl)piperidin-2-yl]-3-hydroxyazetidine-1-carboxylate (180 mg, 0.47 mmol) in ethanol (1 mL) was added acetic acid (53.5 µL, 0.94 mmol) followed by sodium cyanoborohydride (58.7 mg, 0.94 mmol) and the reaction mixture stirred at 70 °C overnight. After cooling to room temperature the suspension was filtered through celite and the solid washed with additional ethanol. The filtrate was concentrated *in vacuo* and taken up in ethyl acetate (30 mL). The organic layer was washed with 2 M sodium hydroxide solution. The sodium hydroxide layer was separated and washed with ethyl acetate (10 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give crude1,1-dimethylethyl 3-hydroxy-3-[6-methyl-1-(phenylmethyl)piperidin-2-yl]azetidine-1-carboxylate as yellow oil (60 mg, 36% yield). Crude product was used further without purification. ^{1}H NMR (400 MHz, $CDCl_3$): 7.22-7.35 (m, 5H), 4.08 (d, 1H), 3.85-3.96 (m, 3H), 3.57 (d, 1H), 3.33-3.36 (m, 1H), 2.91-3.06 (m, 2H), 1.63-1.70 (m, 4H), 1.44 (s, 9H), 1.23 (d,3H), 1.05 (d, 2H); MS (EI) for $C_{21}H_{32}N_2O_3$: 361 (MH^+).

[00456] To a solution of 1,1-dimethylethyl 3-hydroxy-3-[6-methyl-1-(phenylmethyl)piperidin-2-yl]azetidine-1-carboxylate (60 mg, 0.16 mmol) in

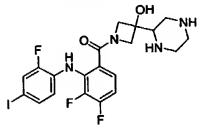
methanol (0.5 mL) was added hydrogen chloride (4N in dioxane, 0.5 mL) and the reaction mixture stirred at 60 °C for one hour. The reaction mixture was cooled to room temperature and concentrated *in vacuo* and aezotroped 3 times from methanol and diethyl ether. On drying the hydrochloride salt of 3-[6-methyl-1-(phenylmethyl)piperidin-2-yl]azetidin-3-ol was obtained as a dark brown residue (40 mg, 81% yield), which was used further without purification. ^{1}H NMR (400MHz, CD_3OD): 7.58-7.63 (m, 2H), 7.47-7.49 (m, 3H), 4.78 (d, 1H), 4.44-4.62 (m, 2H), 4.29 (s, 2H), 4.22-4.26 (m, 1H), 4.12-4.18 (m, 1H), 4.08 (s, 1H), 1.60-2.00 (m, 8H), 1.48 (d, 3H); MS (EI) for $C_{16}H_{25}ClN_2O$: 261 (MH^+).

[00457] To a solution of 3-[6-methyl-1-(phenylmethyl)piperidin-2-yl]azetidin-3-ol hydrochloride (40 mg, 0.13 mmol) in ethyl acetate (3 mL) was added acetic acid (0.5 mL) and Pd/C (50 mg) and the mixture was hydrogenated at 35 psi for 3 hours. The reaction mixture was filtered through celite. The filtrate was concentrated *in vacuo*. The obtained residue was dissolved in a small amount of ethyl acetate and concentrated hydrochloric acid was added and the mixture was concentrated *in vacuo* to give the crude dihydrochloride salt of 3-[6-methylpiperidin-2-yl]azetidin-3-ol (20 mg, 54%). The crude product was used further without purification. ^{1}H NMR (400MHz, CD_3OD): 4.20-4.40 (m, 1H), 4.00-4.10 (m, 1H), 3.60-3.90 (m, 2H), 1.50-2.00 (m, 6H), 1.45 (d, 3H), 1.26-1.30 (m, 1H); MS (EI) for $C_9H_{20}Cl_2N_2O$: 171 (MH^+).

[00458] To a 0 °C solution of 3-[6-methylpiperidin-2-yl]azetidin-3-ol dihydrochloride (20 mg, 0.08 mmol) in DMF (1 mL) was added *N,N*-diisopropylethylamine (42 µL, 0.26 mmol) followed by 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino] benzoyl fluoride (32 mg, 0.08 mmol), prepared using procedures similar to those described in Reference 1, and the reaction mixture stirred at 0 °C for 30 min. The mixture was diluted with acetonitrile and purified by preparative reverse phase HPLC (CH_3CN/H_2O with 0.1% TFA). Fractions were collected and lyophilized to give 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(6-methylpiperidin-2-yl)azetidin-3-ol acetate salt (7 mg, 16% yield) as a white solid. ^{1}H NMR (400MHz, CD_3OD): 7.44-7.50 (m, 1H), 7.34-7.37 (m, 1H), 7.28-7.32 (m, 1H), 7.02-7.12 (m, 1H), 6.60-6.63 (m, 1H), 4.10-4.30 (m, 2H), 3.95-4.09 (m, 2H), 3.80-3.95 (m, 1H), 3.55-3.65 (m, 1H), 3.34-3.36 (m, 1H), 1.90 (s, 3H), 1.62-1.84 (m, 6H), 1.40-1.52 (m, 1H), 1.33 (d, 3H); MS (EI) for $C_{22}H_{23}F_3IN_3O_2$: 546 (MH^+).

EXAMPLE 34

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-piperazin-2-ylazetidin-3-ol



[00459] To a solution of commercially available 1,4-bis(phenylmethyl)piperazine-2,5-dione (2.0 g, 6.8 mmol) in dry THF (50 mL) at -78 °C was added lithium diisopropylamide (2.0 M solution in heptane/THF/ethylbenzene, 3.4 mL, 6.8 mmol). The resulting reddish brown suspension was stirred for 23 min at -78 °C, and then a solution of 1,1-dimethylethyl 3-oxoazetidine-1-carboxylate (770 mg, 4.5 mmol) in THF (10 mL) was added over 30 min by syringe pump. The mixture became a bright yellow solution as it was allowed to warm to room temperature over 3 hours. The mixture was quenched with saturated aqueous ammonium chloride. Water was added to dissolve precipitated salts, and the resulting mixture was extracted twice with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography (60% ethyl acetate: 40% hexanes) to provide 1,1-dimethylethyl 3-[3,6-dioxo-1,4-bis(phenylmethyl)piperazin-2-yl]-3-hydroxyazetidine-1-carboxylate as a colorless foam (1.04 g, 2.23 mmol, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 7.39-7.29 (m, 7H), 7.23-7.19 (m, 3H), 5.34 (d, 1H), 4.82 (d, 1H), 4.58 (d, 1H), 4.37 (d, 1H), 4.37 (d, 1H), 4.22 (d, 1H), 4.15 (s, 1H), 4.08 (d, 1H), 3.97 (d, 1H), 3.75 (d, 1H), 3.74 (d, 1H), 3.67 (d, 1H), 3.64 (br s, 1H), 1.43 (s, 9H).

[00460] A solution of 1,1-dimethylethyl 3-[3,6-dioxo-1,4-bis(phenylmethyl)piperazin-2-yl]-3-hydroxyazetidine-1-carboxylate (1.04 g, 2.2 mmol) in methanol (10 mL) was treated with hydrogen chloride in dioxane (4 N, 5.5 mL, 22 mmol) at 60 °C for 25 min. After cooling to room temperature the solution was concentrated. Ethyl acetate and 2 N hydrochloric acid were added to the residue and the phases were separated. The organic phase was discarded. The aqueous phase was basified with 5 M sodium hydroxide and the resulting solution was extracted 4 times with ethyl acetate. The combined organic extracts were dried over magnesium

sulfate, filtered, and concentrated. The residue was purified by column chromatography (85% dichloromethane: 14% methanol: 1% aqueous ammonium hydroxide) to provide 3-(3-hydroxyazetidin-3-yl)-1,4-bis(phenylmethyl)piperazine-2,5-dione as a colorless film (493 mg, 1.35 mmol, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 7.39-7.28 (m, 6H), 7.25-7.20 (m, 4H), 5.39 (d, 1H), 4.80 (d, 1H), 4.44 (d, 1H), 4.36 (d, 1H), 4.26 (d, 1H), 4.11 (s, 1H), 3.97 (d, 1H), 3.83 (d, 1H), 3.71 (d, 1H), 3.27 (m, 2H); MS (EI) for $C_{21}H_{23}N_3O_3$: 366 (MH^+).

[00461] A solution 3-(3-hydroxyazetidin-3-yl)-1,4-bis(phenylmethyl)piperazine-2,5-dione (493 mg, 1.35 mmol) in ethyleneglycol dimethylether (12 mL) was treated with sodium borohydride (511 mg, 13.5 mmol) followed by slow addition of boron trifluoride-diethyl etherate. The reaction mixture was then heated to reflux for 3 hours. After cooling to 0 °C, methanol (17 mL) was added followed by careful addition of concentrated hydrochloric acid (7 mL). The resulting mixture was heated to reflux for 70 minutes. After cooling to room temperature, insoluble residue was removed by filtration. The filtrate was concentrated to an aqueous mixture of about 10 mL in volume. This mixture was cooled to 0 °C and was then basified to pH 10 with 5 M sodium hydroxide (approximately 17 mL). Dichloromethane (10 mL) was then added followed by di-*tert*-butyl dicarbonate (442 mg, 2.03 mmol). The mixture was warmed to room temperature and stirred for 15 minutes. The layers were separated and the aqueous phase was extracted twice with dichloromethane. The organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography (70% hexanes: 30% ethyl acetate) to provide 1,1-dimethylethyl 3-[1,4-bis(phenylmethyl)piperazin-2-yl]-3-hydroxyazetidine-1-carboxylate as a white foam (408 mg, 0.93 mmol, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 7.35-7.24 (m, 10H), 4.12 (br s, 1H), 3.88 (d, 1H), 3.78-3.65 (m, 4H), 3.53 (d, 1H), 3.43 (d, 1H), 3.21 (m, 1H), 2.80 (br s, 1H), 2.66 (m, 1H), 2.57-2.37 (m, 4H), 1.41 (s, 9H); MS (EI) for $C_{26}H_{35}N_3O_3$: 438 (MH^+).

[00462] To a solution of 1,1-dimethylethyl 3-[1,4-bis(phenylmethyl)piperazin-2-yl]-3-hydroxyazetidine-1-carboxylate (408 mg, 0.93 mmol) in methanol (15 mL) was added 10% palladium on carbon (wet), and the resulting suspension was subjected to an atmosphere of hydrogen for 21 hours. The catalyst was removed by filtration through celite, and the filter cake was rinsed with methanol. The combined filtrate was concentrated to provide 1,1-dimethylethyl 3-hydroxy-3-piperazin-2-ylazetidine-

1-carboxylate as a brown syrup (227 mg, 0.88 mmol, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 3.94-3.76 (m, 5H), 3.12 (m, 1H), 3.01 (m, 1H), 2.94-2.81 (m, 3H), 2.78-2.70 (m, 2H); MS (EI) for $C_{12}H_{23}N_3O_3$: 258 (MH^+).

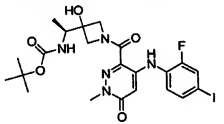
[00463] To a solution of 1,1-dimethylethyl 3-hydroxy-3-piperazin-2-ylazetidine-1-carboxylate (227 mg, 0.88 mmol) and *N,N*-diisopropylethylamine (436 μL, 2.64 mmol) in THF (5 mL) was added 2-nitrobenzenesulfonyl chloride (195 mg, 0.88 mmol). The mixture was stirred at room temperature for 2 hours. The solution was concentrated and the residue was purified by column chromatography (95% dichloromethane: 5% methanol) to provide 1,1-dimethylethyl 3-hydroxy-3-{4-[(2-nitrophenyl)sulfonyl]piperazin-2-yl}azetidine-1-carboxylate as a white foam (308 mg, 0.70 mmol, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 7.98 (m, 1H), 7.72 (m, 2H), 7.64 (m, 1H), 3.96 (d, 1H), 3.94 (d, 1H), 3.85 (d, 1H), 3.79 (d, 1H), 3.79-3.73 (m, 2H), 3.11 (m, 1H), 3.05 (dd, 1H), 3.00 (br s, 1H), 2.94 (dt, 1H), 2.78 (dt, 1H), 2.68 (dd, 1H), 1.45 (s, 9H).

[00464] To a solution of 1,1-dimethylethyl 3-hydroxy-3-{4-[(2-nitrophenyl)sulfonyl]piperazin-2-yl}azetidine-1-carboxylate (308 mg, 0.70 mmol) in methanol (10 mL) was added HCl in dioxane (4 N, 1.75 mL, 7.0 mmol), and the mixture was heated to 60 °C for 30 minutes. The solution was concentrated to provide 3-{4-[(2-nitrophenyl)sulfonyl]piperazin-2-yl}azetidin-3-ol as a sticky white solid. This material was dissolved in dichloromethane (7 mL). To the solution was added *N,N*-diisopropylethylamine (1.16 mL, 7.0 mmol) followed by 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoyl fluoride (277 mg, 0.7 mmol), prepared using procedures similar to those described in Reference 1, and the resulting mixture was stirred at room temperature for 16 hours. The solution was concentrated and the residue was purified by column chromatography (95% dichloromethane: 5% methanol) to provide 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{4-[(2-nitrophenyl)sulfonyl]piperazin-2-yl}azetidin-3-ol as a pale yellow foam (453 mg, 0.63 mmol, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.49 (s, 1H), 7.96 (dd, 1H), 7.71 (m, 2H), 7.53 (dd, 1H), 7.39 (dd, 1H), 7.33 (d, 1H), 7.15 (m, 1H), 6.84 (br s, 1H), 6.62 (m, 1H), 4.29-3.97 (br m, 4H), 3.79-3.62 (m, 3H), 3.26-2.99 (br m, 3H), 2.92-2.62 (br m, 3H); MS (EI) for $C_{26}H_{23}F_3IN_5O_6S$: 718 (MH^+).

[00465] To a solution of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{4-[(2-nitrophenyl)sulfonyl]piperazin-2-yl}azetidin-3-ol (139.4 mg, 0.19 mmol) in DMF (1 mL) was added potassium carbonate (79 mg, 0.57 mmol) and thiophenol (21 μL, 0.21 mmol). The mixture was stirred for 45 min at room temperature then quenched with water. The aqueous mixture was extracted twice with ethyl acetate, and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated. The residue was purified by preparative reverse phase HPLC to provide 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-piperazin-2-ylazetidin-3-ol as a white solid (26.8 mg, 0.05 mmol). ^{1}H NMR (400 MHz, CD_3OD): 7.45 (dd, 1H), 7.36 (m, 1H), 7.32 (m, 1H), 7.03 (m, 1H), 6.62 (ddd, 1H), 4.51 (br dd, 1H), 4.31 (br dd, 1H), 4.17-3.92 (m, 4H), 3.73-3.56 (m, 3H), 3.46 (br m, 1H), 3.26 (m, 1H); MS (EI) for $C_{20}H_{20}F_3IN_4O_2$: 533 (MH^+).

EXAMPLE 36

1,1-Dimethylethyl {(1*S*)-1-[1-({4-[(2-fluoro-4-iodophenyl)amino]-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}carbamate



[00466] To a suspension of 4-[(2-fluoro-4-iodophenyl)amino]-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid (50 mg, 0.13 mmol) in DMF (2 mL), prepared using similar procedures to those described in Reference 4, at room temperature was added 1-hydroxybenzotriazole (36.3 mg, 0.27 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (52 mg, 0.27 mmol) and the reaction was stirred for 2 hours. 1,1-Dimethylethyl [(1*S*)-1-(3-hydroxyazetidin-3-yl)ethyl]carbamate (30 mg, 0.13 mmol), prepared using procedures similar to those in Example 28, and triethylamine (0.04 mL) were added and the mixture was stirred for 15 hours. The reaction mixture was partitioned between saturated sodium chloride and ethyl acetate. The organic layer was washed with 5% lithium chloride solution, saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*

to give crude product as yellow oil. The oil was purified by column chromatography (silica gel, ethyl acetate) to afford 1,1-dimethylethyl {(1*S*)-1-[1-({4-[(2-fluoro-4-iodophenyl)amino]-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}carbamate as a yellow oil (55 mg, 73% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 10.24-10.23 (m, 1H), 7.52-7.50 (m, 2H), 7.12-7.07 (m, 1H), 6.10-6.09 (m, 1H), 5.13-5.09 (m, 1H), 4.91-4.82 (m, 1H), 4.60-4.39 (m, 2H), 4.10-4.08 (m, 1H), 4.00-3.87 (m, 2H), 3.70 (d, 3H), 1.43 (s, 9H), 1.24-1.20 (m, 3H); MS (EI) for $C_{22}H_{27}FIN_5O_5$: 588 (MH^+).

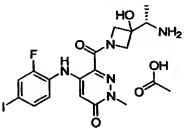
[00467] Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compounds of the invention were prepared:

EXAMPLE 36(a). 1,1-Dimethylethyl {(1*S*)-1-[1-({5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-1-methyl-1*H*-benzimidazol-6-yl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}carbamate: ^{1}H NMR (400 MHz, $CDCl_3$): 7.95 (s, 1H), 7.45-7.44 (m, 1H), 7.33-7.27 (m, 2H), 7.15-7.12 (m, 1H), 6.50-6.47 (m, 1H), 4.82-4.74 (m, 1H), 4.17-3.92 (m, 4H), 3.86 (s, 3H), 3.74-3.60 (m, 1H), 1.40 (s, 9H), 1.11-1.06 (m, 3H). MS (EI) for $C_{25}H_{28}BrClFN_5O_4$: 598 (MH^+) with a chloro, bromo isotope pattern.

EXAMPLE 36(b). 1,1-Dimethylethyl (2*S*)-2-[1-({5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-1-methyl-1*H*-benzimidazol-6-yl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate: MS (EI) for $C_{28}H_{32}BrClFN_5O_4$: 638 (MH^+) with a chloro, bromo isotope pattern.

Example 37

6-({3-[(1*S*)-1-aminoethyl]-3-hydroxyazetidin-1-yl}carbonyl)-5-[(2-fluoro-4-iodophenyl)amino]-2-methylpyridazin-3(2*H*)-one acetate salt



[00468] 1,1-Dimethylethyl {(1*S*)-1-[1-({4-[(2-fluoro-4-iodophenyl)amino]-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl}carbonyl)-3-hydroxyazetidin-3-

yl]ethyl}carbamate (55 mg, 0.09 mmol), prepared using procedures similar to those described in Example 36, was taken up in methanol (2 mL) and hydrochloric acid (4N in dioxane, 1 mL, 4 mmol) was added and the reaction was stirred at 60 °C for 2 hours. The reaction mixture was concentrated *in vacuo* and was purified by reverse-phase HPLC followed by lyophilization of the pure fractions to afford 6-({3-[(1*S*)-1-aminoethyl]-3-hydroxyazetidin-1-yl}carbonyl)-5-[(2-fluoro-4-iodophenyl)amino]-2-methylpyridazin-3(2*H*)-one acetate as yellow solid (40 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): 10.17 (d, 1H), 7.52-7.46 (m, 2H), 7.09 (t, 1H), 6.13-6.12 (m, 1H), 4.51-4.48 (m, 2H), 4.18-4.03 (m, 2H), 3.73 (d, 3H), 3.35-3.28 (m, 1H), 3.22-2.80 (br, 3H), 1.21-1.19 (m, 3H); MS (EI) for $C_{17}H_{19}FIN_5O_3$: 488 (MH^+).

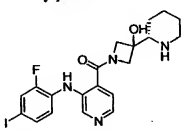
[00469] Using the same or analogous synthetic techniques and/or substituting with alternative reagents, the following compounds of the invention were prepared:

Example 37(a). 3-[(1*S*)-1-Aminoethyl]-1-({5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-1-methyl-1*H*-benzimidazol-6-yl}carbonyl)azetidin-3-ol hydrochloride. MS (EI) for $C_{20}H_{20}BrClFN_5O_2$: 498 (MH^+) with a chloro, bromo isotope pattern

Example 37(b). 1-({5-[(4-Bromo-2-chlorophenyl)amino]-4-fluoro-1-methyl-1*H*-benzimidazol-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol hydrochloride. ^{1}H NMR (400 MHz, CD_3OD): 9.42 (s, 1H), 7.97-7.96 (m, 1H), 7.57 (s, 1H), 7.30-7.27 (m, 1H), 6.70-6.66 (m, 1H), 4.60-4.55 (m, 1H), 4.28 (t, 1H), 4.19 (s, 3H), 4.13-3.98 (m, 2H), 3.38-3.32 (m, 2H), 3.00 (t, 1H), 1.86-1.30 (m, 6H). MS (EI) for $C_{23}H_{24}BrClFN_5O_2$. HCl: 538 (MH^+) with a chloro, bromo isotope pattern

EXAMPLE 38

1-({3-[(2-fluoro-4-iodophenyl)amino]pyridin-4-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol



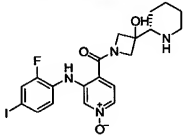
[00470] 3-[(2-Fluoro-4-iodophenyl)amino]pyridine-4-carboxylic acid (200 mg, 0.559 mmol), prepared using procedures similar to those described in WO 2006/045514, was suspended in DMF (7 mL) and 1-hydroxybenzotriazole (151 mg,

1.12 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (214 mg, 1.12 mmol) were added. The mixture was stirred at ambient for 10 minutes and then triethylamine (0.078 mL, 0.559 mmol) was added. After a further 20 minutes, 1,1-dimethylethyl (2*S*)-2-(3-hydroxyazetidin-3-yl)piperidine-1-carboxylate (143 mg, 0.559 mmol), prepared using similar procedures to those described in Example 22(a) and 22(b), and triethylamine (0.16 mL, 1.15 mmol) were added and the mixture was stirred for 15 hours. The mixture was partitioned between ethyl acetate and saturated ammonium chloride. The organic portion was washed with 5% lithium chloride and twice with saturated sodium bicarbonate, then was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 60-80% ethyl acetate in hexanes) to give 1,1-dimethylethyl (2*S*)-2-[1-({3-[(2-fluoro-4-iodophenyl)amino]pyridin-4-yl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate (368 mg, 0.587 mmol, 74% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 8.73 (br m, 1H), 8.62 (br s, 1H), 8.14 (d, 1H), 7.47 (dd, 1H), 7.43-7.39 (m, 1H), 7.20-7.12 (m, 2H), 4.38-4.21 (m, 2H), 4.16-4.01 (m, 2H), 4.01-3.88 (m, 1H), 3.44-3.30 (m, 1H), 2.98-2.83 (m, 1H), 2.00-1.88 (m, 1H), 1.71-1.50 (m, 6H), 1.44 (s, 9H); MS (EI) for $C_{25}H_{30}FIN_4O_4$: 597 (MH^+).

[00471] 1,1-Dimethylethyl (2*S*)-2-[1-({3-[(2-fluoro-4-iodophenyl)amino]pyridin-4-yl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate (24 mg, 0.040 mmol) was dissolved in methanol (2 mL) and treated with 4 N hydrochloric acid in dioxane (0.25 mL, 1 mmol) at reflux for 20 minutes. The mixture was concentrated *in vacuo* and was purified by reverse-phase HPLC followed by lyophilization of the pure fractions to afford 1-({3-[(2-fluoro-4-iodophenyl)amino]pyridin-4-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol acetate (14 mg, 0.025 mmol, 63% yield): ^{1}H NMR (400 MHz, d_6-DMSO): 8.62 (br s, 1H), 8.46 (s, 1H), 8.18 (dd, 1H), 7.65 (dd, 1H), 7.45 (d, 1H), 7.37 (t, 1H), 7.16-7.08 (m, 1H), 4.25 (dd, 1H), 4.04 (dd, 1H), 3.90 (t, 1H), 3.70 (d, 1H), 2.95 (br d, 1H), 2.52-2.42 (m, 2H), 1.78-1.68 (m, 1H), 1.57 (br t, 1H), 1.47 (br d, 1H), 1.35-1.13 (m, 2H), 1.10-0.96 (m, 1H); MS (EI) for $C_{20}H_{22}FIN_4O_2$: 497 (MH^+).

EXAMPLE 39

1-({3-[(2-fluoro-4-iodophenyl)amino]-1-oxidopyridin-4-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol

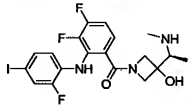


[00472] 1,1-Dimethylethyl (2*S*)-2-[1-({3-[(2-fluoro-4-iodophenyl)amino]pyridin-4-yl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate (80 mg, 0.134 mmol), prepared using procedures similar to those described in Example 38, was dissolved in dichloromethane (3 mL) and treated with 3-chloroperoxybenzoic acid (73% pure; 32 mg, 0.135 mmol) at ambient for 7 hours. 3-chloroperoxybenzoic acid (73% pure; 32 mg, 0.135 mmol) was added and the mixture was stirred for 15 hours. The mixture was purified by column chromatography (silica gel, 0-10% ethanol in ethyl acetate) to give 1,1-dimethylethyl (2*S*)-2-[1-({3-[(2-fluoro-4-iodophenyl)amino]-1-oxidopyridin-4-yl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate (57 mg, 0.093 mmol, 69% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 9.38 (s, 1H), 8.00 (s, 1H), 7.68 (dd, 1H), 7.51 (dd, 1H), 7.46 (d, 1H), 7.19 (br d, 1H), 7.09 (t, 1H), 5.78 (br, 1H), 4.44-3.98 (m, 3H), 3.98-3.87 (m, 1H), 3.49-3.39 (m, 1H), 3.07-2.88 (m, 1H), 2.01-1.91 (m, 1H), 1.70-1.47 (m, 6H), 1.45 (s, 9H); MS (EI) for $C_{25}H_{30}FIN_4O_5$: 613 (MH^+).

[00473] 1,1-Dimethylethyl (2*S*)-2-[1-({3-[(2-fluoro-4-iodophenyl)amino]-1-oxidopyridin-4-yl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate (57 mg, 0.093 mmol) was dissolved in methanol (2 mL) and treated with 4N hydrochloric acid in dioxane (0.25 mL, 1 mmol) at 50 °C for 2.25 hours. The mixture was concentrated *in vacuo* and was purified by reverse-phase HPLC followed by lyophilization of the pure fractions to afford 1-({3-[(2-fluoro-4-iodophenyl)amino]-1-oxidopyridin-4-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol acetate (35 mg, 0.061 mmol, 66% yield): ^{1}H NMR (400 MHz, d_6-DMSO): 7.83 (s, 1H), 7.72 (dt, 2H), 7.55-7.51 (m, 1H), 7.47-7.41 (m, 1H), 7.24 (t, 1H), 4.45-4.32 (m, 1H), 4.14-3.95 (m, 2H), 3.72 (d, 1H), 2.97 (d, 1H), 2.58-2.43 (m, 2H), 1.80-1.73 (m, 1H), 1.67-1.55 (m, 1H), 1.49 (br d, 1H), 1.38-1.16 (m, 2H), 1.16-1.01 (m, 1H); MS (EI) for $C_{20}H_{22}FIN_4O_3$: 513 (MH^+).

EXAMPLE 40

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(1*S*)-1-(methylamino)ethyl]azetidin-3-ol



[00474] To 3-[(1*S*)-1-aminoethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol (87.4 mg, 0.18 mmol), prepared using similar procedures to those described in Example 28, was added formaldehyde (37% aqueous, 14 mg, 0.18 mmol) in methanol (2 mL) and sodium borohydride (7 mg, 0.18 mmol). The mixture was stirred for 3 h at rt, after which sodium borohydride (16 mg, 0.42 mmol) was added. Upon stirring an additional 1.25 h, more formaldehyde (37% aqueous, 1 drop) was added, and the mixture was stirred 3 days at rt. A further small spatula (~50 mg) of sodium borohydride was then added, and the mixture was stirred at rt for 30 min. After quenching with 1 N HCl, the reaction mixture was purified directly by preparative HPLC. The clean material was converted to its hydrochloride salt to provide 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(1*S*)-1-(methylamino)ethyl]azetidin-3-ol as a yellow solid (21.7 mg, 0.040 mmol, 22% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (dd, 1H), 7.36 (d, 1H), 7.31 (m, 1H), 7.06 (q, 1H), 6.62 (dt, 1H), 4.36 (dd, 1H), 4.21-3.91 (m, 3H), 3.44 (q, 1H), 2.66 (s, 3H), 1.29 (br m, 3H); MS (EI) for $C_{19}H_{19}F_3IN_3O_2$: 506 (MH^+).

Biological Example 1

Biochemical Assay

[00475] For a biochemical measurement of MEK1 inhibitory activity, compounds of the invention were screened in a triple coupled cRaf-MEK-ERK2 assay using ALPHASCREEN (Registered Trademark of Perkin Elmer) technology (Perkin Elmer). The compound of the invention, 0.5 μL of 100% DMSO stock solution, is diluted into an assay buffer composed of 20 mM Tris (pH = 7.5), 10 mM magnesium chloride, 0.03% CHAPS and 1 mM DTT. Subsequently, 10 μL of substrate mixture is added composed of unactive MEK1 (3 nM), ATP (50 μM), unactive ERK2 (4 nM),

biotinylated MBP peptide (b-FFKNIVTPRTPPPSQGK, 1 μM) and antiphospho MBP peptide (0.5 nM). The mixture is then gently shaken for 30 minutes at room temperature followed by addition of active cRaf (5 μL at 0.5 nM) to initiate reaction. The mixture is then shaken for 100 minutes at room temperature then quenched by addition of 10 μL of a mixture of 5μg/mL streptavidin donor beads and 5μg/mL protein A acceptor beads in detection buffer (75 mM Hepes pH = 7.5, 300 mM sodium chloride, 120 mM EDTA, 0.3% BSA and 0.03% Tween), followed by incubation overnight and signal detection on an ALPHAQuest® (Registered Trademark of Perkin Elmer) plate reader (Perkin Elmer).

[00476] Compounds of the invention are inhibitors of MEK. The extent to which these compounds are MEK inhibitors can be determined by one of ordinary skill in the art. In particular, the compounds can be tested in the assay described in Biological Example 1. When tested in that assay, compounds of the invention demonstrated the ability to bind to MEK. In one embodiment of the invention, the MEK inhibitor is selected from the compounds in Table 1 having a MEK-binding affinity of about 4 μM or less. In another embodiment, the MEK inhibitor is selected from the compounds in Table 1 having a MEK-binding affinity of about 3 μM or less. In another embodiment, the MEK inhibitor is selected from the compounds in Table 1 having a MEK-binding affinity of about 2 μM or less. In another embodiment, the MEK inhibitor is selected from the compounds in Table 1 having a MEK-binding affinity of about 1.6 μM or less. In another embodiment, the MEK inhibitor is selected from the compounds in Table 1 having a MEK-binding affinity of about 1 μM or less. In another embodiment, the MEK inhibitor is selected from the compounds in Table 1 having a MEK-binding affinity of about 0.7 μM or less. In another embodiment, the MEK inhibitor is selected from the compounds in Table 1 having a MEK-binding affinity of about 0.3 μM or less. In another embodiment, the MEK inhibitor is selected from the compounds in Table 1 having a MEK-binding affinity of about 0.2 μM or less. In another embodiment, the MEK inhibitor is selected from the compounds in Table 1 having a MEK-binding affinity of about 0.1 μM or less. In another embodiment, the MEK inhibitor is selected from the compounds in Table 1 having a MEK-binding affinity of about 0.05 μM or less.

Biological Example 2

Endogenous ERK Phosphorylation ELISA Assay

[00477] MDA-MB-231T (ATCC), Calu-6 (ATCC), HCT 116 (ATCC), A2058 (ATCC), and A375 (ATCC) cells were seeded at 20000, 30000, 30000, 20000, and 30000 cells/well, respectively, onto black 96-well microtiter plates (Costar 3904), in DMEM (Cellgro) containing 10% FBS (Heat-Inactivated, Cellgro), 1% NEAA (Cellgro), and 1% Pen/Strep (Cellgro). SK-MEL-28 (ATCC) cells were seeded at 20000 cells/well in MEM (ATCC) containing 10% FBS (Heat-Inactivated, Cellgro), and 1% Pen/Strep (Cellgro). The cells were then incubated at 37°C, 5% CO_2 for 24 h. Serum starvation was performed by replacing the medium with serum-free DMEM or MEM for an additional 24 h. Serial dilutions of test compounds in fresh serum-free medium in a final concentration of 0.3% DMSO (vehicle) were added to the cells and incubated for 1 h. Negative control wells were in serum-free medium + 0.3% DMSO only. After treatment, the medium was removed and cells were fixed with 4% formaldehyde, followed by quenching of endogenous peroxidases with 0.6% H_2O_2. Plates were then blocked (10% FBS, Cellgro) and incubated with mouse monoclonal anti-phospho-p44/42 MAPK, E10 (1:2000, Cell Signaling), followed by secondary antibody (HRP-conjugated, goat anti-mouse IgG, 1:3000 from Jackson ImmunoResearch Laboratories, Inc). Washing of the plates was performed with PBS-T (0.1% Triton X-100) in between all incubation steps. A luminol-based substrate solution was then added and plates read using the Victor Wallac machine. IC_{50} values were determined based on total ERK phosphorylation with compound treatment versus total ERK phosphorylation with 0.3% DMSO treatment alone.

Biological Example 3
BrdU Cell Proliferation Assay

[00478] MDA-MB-231T (ATCC), Calu-6 (ATCC), HCT 116 (ATCC), A2058 (ATCC), A375 (ATCC), and Colo-205 (ATCC) cells were plated at densities of 2500, 3500, 3500, 2500, 3500, and 15000 cells/well onto 96-well microtiter plates (Cat# 3904, Costar), in DMEM (Cellgro) containing 10% FBS (Heat Inactivated, Cellgro), 1% Pen/Strep (Cellgro), and 1% NEAA (Cellgro). SK MEL-28 (ATCC) and WM-266-4 (ATCC) were plated at densities of 2000 and 6000 cells/well in MEM (ATCC) containing 10% FBS (Heat-Inactivated, Cellgro), and 1% Pen/Strep (Cellgro). The cells were incubated overnight at 37°C, 5% CO_2 for 18 h. The next day, cells were

treated with a serial dilution of compound in medium (containing a final concentration of 0.3% DMSO). Triplicate wells were used for each compound concentration. The control wells received 0.3% DMSO media. The cultures were incubated at 37°C, 5% CO_2 for an additional 48 h. The cells were assayed for proliferation according to the "Cell Proliferation ELISA, Bromo Deoxyuridine (BrdU) (chemiluminescence) kit" from Roche. The cells were treated with the BrdU labeling solution and then fixed with FixDenat solution. Anti-BrdU-POD (PerOxiDase) conjugate was added to the cells, after which the plates were washed 3x with 1X PBS. Substrate solution was added, and the plates were read for luminescence using the Victor Wallac machine. IC_{50} values were calculated based on the cell proliferation with compound treatment compared to the vehicle control.

Biological Example 4

In vivo mouse models

[00479] The ability of a MEK inhibitor, administered as monotherapy (i.e. not in combination with another cancer treatment), to inhibit the growth of the following tumors in mice was examined. The models can also be used by one of ordinary skill in the art to determine the desirability of a particular combination of a MEK inhibitor with another cancer treatment.

[00480] Female athymic nude mice (NCr) 5-8 weeks of age and weighing approximately 20g were purchased from Taconic (Germantown, NY). Prior to initiation of a study, the animals were allowed to acclimate for a minimum of 48 h. During these studies, animals were provided food and water ad libitum and housed in a room conditioned at 70-75°F and 60% relative humidity. A 12 h light and 12 h dark cycle was maintained with automatic timers.

[00481] Colo-205 human colorectal carcinoma cells were cultured in vitro in DMEM (Mediatech) supplemented with 10% Fetal Bovine Serum (Hyclone), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified, 5% CO_2 atmosphere. On day 0, cells were harvested by trypsinization, and $3x10^6$ cells (passage #3, 92% viability) in 0.1 ml ice-cold Hank's balanced salt solution were implanted intradermally in the hind-flank of 5-8 week old female athymic nude mice.

[00482] A375 human melanoma cells were cultured in vitro in DMEM (Mediatech) supplemented with 10% Fetal Bovine Serum (Hyclone), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified, 5% CO_2 atmosphere. On day 0,

cells were harvested by trypsinization, and $5x10^6$ cells (passage #8, >99% viability) in 0.1 mL ice-cold Hank's balanced salt solution were implanted intradermally in the hind-flank of 5-8 week old female athymic nude mice.

[00483] A2058 human melanoma cells were cultured in vitro in DMEM (Mediatech) supplemented with 10% Fetal Bovine Serum (Hyclone), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified, 5% CO_2 atmosphere. On day 0, cells were harvested by trypsinization, and $3x10^6$ cells (passage #5, 80% viability) in 0.1 mL ice-cold Hank's balanced salt solution were implanted intradermally in the hind-flank of 5-8 week old female athymic nude mice.

[00484] MDA-MB-231 human breast adenocarcinoma cells were cultured in vitro in DMEM (Mediatech) supplemented with 10% Fetal Bovine Serum (Hyclone), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified, 5% CO_2 atmosphere. On day 0, cells were harvested by trypsinization, and $1x10^6$ cells (passage #6, >99% viability) in 0.1 mL ice-cold Hank's balanced salt solution were implanted subcutaneously into the mammary fat pad of 5-8 week old female athymic nude mice.

[00485] Calu-6 human lung anaplastic carcinoma cells were cultured in vitro in DMEM (Mediatech) supplemented with 10% Fetal Bovine Serum (Hyclone), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified, 5% CO_2 atmosphere. On day 0, cells were harvested by trypsinization, and $5x10^6$ cells (passage #8, 96% viability) in 0.1 mL ice-cold Hank's balanced salt solution were implanted intradermally in the hind-flank of 5-8 week old female athymic nude mice.

[00486] For subcutaneous or intradermal tumors, the mean tumor weight of each animal in the respective control and treatment groups was determined twice weekly during the study. Tumor weight (TW) was determined by measuring perpendicular diameters with a caliper, using the following formula: tumor weight (mg) = [tumor volume = length (mm) x width^2 (mm^2)]/2.

[00487] Percent inhibition of tumor growth (TGI) is determined with the following formula:

$$\left[1 - \left[\frac{(X_f - X_0)}{(Y_f - X_0)}\right]\right] * 100$$

where X_0 = average TW of all tumors on group day; X_f = TW of treated group on Day f; Y_f = TW of vehicle control group on Day f

[00488] If tumors regress below their starting sizes, then the percent tumor regression is determined with the following formula:

$$\left[\frac{(X_0 - Xf)}{X_0}\right] * 100$$

TGI is calculated individually for each tumor to obtain a mean ± SEM value for each experimental group. Statistical significance is determined using the 2-tailed Student's t-test (significance defined as $P<0.05$).

Biological Example 5

WM-266-4 Human Melanoma Xenograft Model

[00489] The WM-266-4 human melanoma cell line is PTEN-deficient, and harbors a heterozygous activating mutation in the gene encoding B-Raf. Therefore, the ability of a MEK inhibitor administered as monotherapy, and in combination with the mTOR inhibitor rapamycin, was examined to inhibit the growth of WM-266-4 xenograft tumors in nude mice.

[00490] Tumors were established in female nude mice and staged when the tumors reached 112 ± 6 mg. The MEK compound was dosed orally (in the morning) at 10 mg/kg qd and rapamycin dosed intraperitoneally (in the afternoon, ~7 h after the morning dose) at 5 mg/kg qd were administered as single agents or in combination. The MEK compound administered as monotherapy caused significant tumor growth inhibition Coadministration of rapamycin and the MEK compound resulted in efficacy significantly superior ($p < 0.001$) to that achieved with either agent given alone (95% TGI, compared with TGI of 60% and 82%).

Summary of Growth Inhibition of WM-266-4 Tumors by a MEK Inhibitor Administered Alone or in Combination with Rapamycin

AM Test Article	Dose (qd x 14)	PM Test Article	Dose	Schedule	TGI[a] (%)	P value (vs. Veh)
Vehicle	10 mL/kg PO	Vehicle	10 mL/kg IP[b]	qd x 14	-	-
MEK compound	10 mg/kg PO	Vehicle	10 mL/kg IP	qd x 14	82	2.67E-09
Vehicle	10 mL/kg PO	Rapamycin	5 mg/kg IP	qd x 14	60	1.39E-06
MEK compound	10 mg/kg PO	Rapamycin	5 mg/kg IP	qd x 14	95	1.29E-10

[a]TGI, tumor growth inhibition; [b]IP, administered intraperitoneally.

Pharmaceutical Composition Examples

[00491] The following are representative pharmaceutical formulations containing a compound of Formula I.

Tablet Formulation

The following ingredients are mixed intimately and pressed into single scored tablets.

Ingredient	Quantity per tablet, mg
compound of this invention	400
Cornstarch	50
croscarmellose sodium	25
Lactose	120
magnesium stearate	5

Capsule Formulation

The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

Ingredient	Quantity per tablet, mg
compound of this invention	200
lactose, spray-dried	148
magnesium stearate	2

Suspension Formulation

The following ingredients are mixed to form a suspension for oral administration.

Ingredient	Amount
compound of this invention	1.0 g